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Thallium (Tl) is a highly toxic metal that is anthropogenically concentrated in the environment. Tl toxicity and the quantitative analysis of trace levels of Tl in biologic materials by atomic absorption spectroscopy is reviewed; a study designed to evaluate the antidotal efficacy of 2 compounds in the treatment of acute Tl toxicity in rats is documented. Unithiol (2,3-dimercapto-1-propanesulfonic acid, DMPS) and prussian blue (potassium ferric hexacyanoferrate(II), PB), given alone and in combination, were evaluated as antidotes in the treatment of acute thallotoxicosis in male Sprauge-Dawley rats. The relative accumulation of Tl in organs was kidney>>heart>liver=brain. PB induced significant decorporation of Tl from all tissues. DMPS failed to significantly decrease the Tl content in any organ, but significantly decreased the Tl content in whole blood. PB+DMPS treatment significantly decreased the Tl content in all organs, but to no greater extent than PB alone. PB and PB+DMPS treatments significantly increased the Tl content of feces, whereas DMPS treatment alone produced little

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THALLIUM TOXICITY:
THE PROBLEM; AN ANALYTICAL APPROACH; AN ANTIDOTAL STUDY

by

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A THESIS

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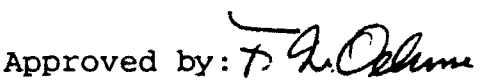
Approved by: 

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ABSTRACT

Thallium (Tl) is a highly toxic metal that is anthropogenically concentrated in the environment. Chapter 1 and 2 review Tl toxicity and the quantitative analysis of trace levels of Tl in biologic materials by atomic absorption spectroscopy (AAS). Chapter 3 documents a study designed to evaluate the antidotal efficacy of 2 compounds in the treatment of acute Tl toxicity in rats. The treatment objective in Tl poisoning is to enhance the metal's elimination from the body without promoting redistribution to target organs, particularly the brain. The therapeutic efficacy of many heavy-metal chelators have been investigated for Tl poisoning; all have some limiting feature. Unithiol (2,3-dimercapto-1-propanesulfonic acid, DMPS) and prussian blue (potassium ferric hexacyanoferrate (II), PB), given alone and in combination, were evaluated as antidotes in the treatment of acute thallotoxicosis in male Sprauge-Dawley rats. Animals were poisoned with equivalent doses of 20 mg Tl/kg BW po on day 0, using thallous sulfate. On day 1 (24 h later), antidotal treatments began and were continued through day 4 as follows: 50 mg PB/kg BW po, 2/d; 5 mg DMPS/kg BW ip, 6/d (day 1), 4/d (day 2), 2/d (days 3-4); or their combination. Animals were sacrificed by ip injection of sodium phenobarbital 24 h after the last antidotal treatment (day 5) and tissue samples collected. Thallium concentrations in kidney, liver, heart, brain, whole blood and feces were determined by electrothermal

atomic absorption spectroscopy. The relative accumulation of Tl in organs was kidney>>heart>liver≈brain. PB induced significant decorporation of Tl from all tissues. DMPS failed to significantly decrease the Tl content in any organ, but significantly decreased the Tl content in whole blood. PB+DMPS treatment significantly decreased the Tl content in all organs, but to no greater extent than PB alone. PB and PB+DMPS treatments significantly increased the Tl content of feces, whereas DMPS treatment alone produced little effect. This study indicates that PB is a beneficial antidote in the treatment of acute thallotoxicosis in rats. The failure of DMPS to significantly decrease the Tl content in 4 target organs suggests it would not be useful in the treatment of Tl poisoning.

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INTRODUCTION

Thallium is a highly toxic metal normally present at trace levels in the environment except when concentrated by human activities. Chapter 1 explores the problem of Tl poisoning in animals and humans. The chemistry relevant to Tl toxicity is presented. The metal's occurrence and distribution and its production and uses are briefly introduced, followed by a discussion of its absorption, distribution and excretion in mammals. The molecular basis of Tl toxicity is reviewed to provide a biochemical and physiological basis for understanding the clinical manifestations of Tl poisoning. A review of the metal's clinical toxicology follows, with emphasis placed on the major effects caused by acute Tl toxicity. Thallotoxicosis often is a diagnostic challenge; clinical clues and laboratory tests useful in diagnosis of Tl poisoning are presented. The management of thallotoxicosis is discussed and treatment options and considerations are presented.

The analytical challenge in toxic-metal antidote studies is the accurate quantification of trace levels of the offending metal in complex biologic matrices (ie, organs, blood, feces, etc). Atomic absorption spectroscopy (AAS) fills this need. Since its introduction by Walsh more that 30 years ago, AAS has matured to become the dominant analytical method for trace level metal analysis in the clinical laboratory.

Chapter 2 discusses the basic principles and instrumentation of AAS. Sample preparation techniques are discussed; destruction of organic matter and liquid-liquid separations are emphasized. The application of flame and graphite furnace (electrothermal) AAS to the determination of Tl in biologic materials is reviewed.

Chapter 3 details my research project, which involved the evaluation of the antidotal efficacy of 2 compounds in the treatment of acute Tl toxicity in rats. The treatment objective in Tl poisoning is to enhance the metal's elimination from the body without promoting redistribution to target organs, particularly the brain. To this end, the therapeutic efficacy of different metal chelators has been investigated in the attempt to find an effective antidote for thallotoxicosis. To date, no chelator has proven to be totally satisfactory.

A metal chelator, Unithiol (2,3-dimercapto-1-propanesulfonic acid, DMPS), and an inorganic dye, prussian blue (potassium ferric hexacyanoferrate(II), PB), given alone and in combination, were evaluated as antidotes in the treatment of acute thallotoxicosis in male Sprauge-Dawley rats. Thallium concentrations in kidney, liver, heart, whole blood and feces were determined by electrothermal AAS. This study indicates that PB is a beneficial antidote in the treatment of acute thallotoxicosis in rats. The failure of DMPS to significantly decrease the Tl content in 4 target organs

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CHAPTER 1

A REVIEW OF THALLIUM TOXICITY

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ABSTRACT

Thallium (Tl) is one of the most toxic of the heavy metals. Its continued use as a rodenticide in many developing countries and its increasing use in an expanding number of new technologies raise concerns about exposure risk to animals and humans. Because Tl and potassium (K) have the same charge and similar ionic radii, Tl follows K distribution patnways and alters a number of K-dependent processes. Possible toxic mechanisms of Tl include ligand formation with protein sulfhydryl groups, inhibition of cellular respiration, interaction with riboflavin and riboflavin-based cofactors, and disruption of calcium homeostasis. The principal clinical features of thallotoxicosis are gastroenteritis, peripheral neuropathy of unknown etiology, and alopecia. The presence of elevated Tl levels in the urine or other biologic materials confirms the diagnosis of Tl poisoning. Treatment with prussian blue (or activated charcoal) will interrupt the enterohepatic cycling of Tl, thus enhancing fecal elimination of the metal. Forced diuresis with potassium loading will increase the renal clearance of Tl, but should be used cautiously because neurologic and cardiovascular symptom may be exacerbated. If recognized and treated early, Tl poisoning carries a favorable prognosis for full recovery.

KEYWORDS: Thallium; poison; treatment; chelator; prussian blue; ferric hexacyanoferrate(II); neuropathy; alopecia.

The toxicity of thallium (Tl) has been known almost since its discovery by Crookes in 1861. While spectroscopically examining the flue dust from a sulfuric acid production plant for tellurium, he noted an unexpected bright green line in the emission spectrum. Crookes attributed the line to a new element which he named "thallium", from the Latin *thallos*, meaning young twig or shoot (1). The following year, Lamy, a contemporary of Crookes, experienced lassitude and weakness while working to isolate the metal. Suspecting Tl to be toxic, he gave thallium sulfate (Tl_2SO_4) to dogs, ducks and hens, all of whom died within a few days (2). Today Tl is recognized as one of the most toxic of the heavy metals (LD_{50} 8-12 mg/kg, man; LD_{50} 30 mg/kg, rats) (3,4). The lethality of Tl salts are listed in Table 1.

CHEMISTRY

Freshly-prepared Tl has metallic luster that soon develops a bluish-grey tinge when exposed to air, the result of oxide build-up on its exposed surface. In the presence of water, the hydroxide is formed. Metallic Tl is soft and malleable, similar to lead in both appearance and physical properties. Some of the element's physical constants are listed in Table 2.

Thallium is located between mercury and lead in the periodic table and is classified along with boron (non-metal),

aluminum, gallium, and indium as a Group IIIA element. The metals of this group are electropositive; as their atomic weights increase, so does their basic character. The monovalent Tl cation (Tl^+) is considered a soft acid (as are cadmium [Cd^{2+}], methylmercury [CH_3Hg^+] and [Hg^{2+}]). Under the Pearson classification of hard and soft acids and bases, hard metals favor interactions with hard bases, and soft metals favor interactions with soft bases (5). Since Tl^+ is considered to be a soft acid, it tends to form stable complexes with soft ligand donors such as sulfur-containing compounds (6).

Salts of the Group IIIA metals are water soluble, but readily hydrolyze at pH≥7 to form insoluble hydroxides, except for Tl salts (7). Indeed, the high solubility of Tl salts (ie, Tl sulfate, nitrate and acetate) is an important physical property contributing to their marked toxicity in animals and humans.

The electron configuration of Tl is $[Xe]4f^{14}5d^{10}6s^26p$. Its s electrons show a low propensity to be released or covalently bound, so the metal occurs predominantly in the monovalent form. The oxidation potential of the reaction $Tl^+ + 2e^- \rightarrow Tl^{3+}$ is +1.25 V; for $Tl^+ + e^- \rightarrow Tl^\circ$ it is -0.34 V (8).

Thallium and the alkali metals (potassium [K] and cesium) possess similar ionic radii and electronegativity constants. These properties and its position in the periodic table give Tl a distinct chalcophilic and, occasionally, siderophilic character.

Inorganic Tl(I) compounds are more stable than the Tl(III) analogues in aqueous solution at neutral pH. In contrast, covalent organothallium compounds are stable only in the trivalent form. Tl^{3+}, but not Tl^{+}, can be methylated by methyl-vitamin B_{12} (9). The chemistry of Tl (1) and the Group IIIA metals (10,11) has been reviewed.

OCCURRENCE AND DISTRIBUTION

Thallium is distributed widely, but it is generally present in very low concentration. The crustal abundance of Tl is 0.3 ppm, with higher levels found in granite, shale and manganese nodules. It has also been detected in volcanic rocks, meteorites and in plants. Since Tl and potassium possess similar ionic radii, Tl is concentrated in magmatic potassium minerals such as feldspars and micas. The few Tl minerals that exist contain between 16% and 60% Tl and are quite rare: Crooksite $(Cu,Tl,Ag)_2Se$; lorandite $TlAsS_3$; hutchinsonite $(Tl,Ag)_2S.PbS.2As_2S_3$; and vrbaite $Tl_2S3(As,Sb)_2S_3$ (1). Natural Tl concentrations in seawater and freshwater are estimated to be <0.03 ppb (3). Thallium levels in normal humans and animals are <1 ppb in blood and urine and <10 ppb in tissues (4,12).

PRODUCTION AND USES

Thallium is found in pyrites used to make sulfuric acid; the H_2SO_4 production process generates waste residue that yields commercially recoverable levels of the element. Thallium is concentrated in iron, lead, cadmium and copper smelters as flue dust which is further processed to recover commercial quantities of the metal. Annual worldwide Tl production is only ~5 tons (13); recent US production is estimated to be 1500 lbs (682 kg). Thallium is also released to the environment by cement plant emissions and through agricultural use of phosphate fertilizer (14).

A small amount of Tl is used in alloys (anticorrosive), optical lenses (increases refractive index), low-temperature thermometers, dye and pigments (artist paints), semiconductors, superconducting ceramics and films, fiber optic cables, vapor lamps, scintillation counters, portable radiation (γ ray) detection devices, and in organic chemistry (catalyst) (8,15,16).

Mining and smelting, together with sulfuric acid production and coal-burning power plants, are the major iatrogenic sources of Tl in the environment (17,18). Major non-point sources are auto emissions (urban) and phosphate fertilizer (rural), but their contribution to the total environmental burden of the metal has not been fully assessed. The use of Tl in these commercial applications gives rise to

concerns about occupational exposure and environmental pollution (19).

Thallium sulfate (Tl_2SO_4), an odorless and tasteless compound, was once used in the US as an insecticide/rodenticide, but was restricted in 1975 as a consequence of several highly publicized accidental, criminal and suicidal poisonings (2,20). Many developed countries have banned or strictly controlled its use for this purpose (21), yet poisonings still too frequently occur. Its uncontrolled use in developing countries has resulted in a number of accidental human and animal poisonings (22-24).

Thallium was once used to treat syphilis, gonorrhea, tuberculosis, ringworm infestation of the scalp, and as a cosmetic epilant. Safer and more efficacious drugs long ago replaced Tl in the treatment of these conditions. The only medical use of Tl today is as a radioactive contrast agent (^{201}Tl) to image tumors and to visualize the heart in myocardial function tests (25,26).

ABSORPTION, DISTRIBUTION AND EXCRETION

After rapid and complete absorption from the respiratory or gastrointestinal (GI) tract or skin, water-soluble Tl salts are widely distributed to organs and tissues, including the brain, heart, kidney, skeletal muscle and testis, the principal targets of Tl toxicity (27). Since Tl^+ (1.50 Å) and K^+

(1.38 Å) are univalent ions with similar ionic radii, Tl^+ interferes with K^+-dependent processes and mimics K^+ in its movement and intracellular accumulation in mammals (28). The thallium cation is less rapidly released than the potassium cation (K^+) once it moves into the cell. Because of its large distribution volume and low free plasma concentration, renal excretion of Tl is slow and it may be detected for months after exposure in untreated persons. In mammals, its body clearance is exponential with an estimated half-life of 4 d (29). The kidneys filter Tl into the urine, the salivary glands and liver concentrate Tl in their secretions, and the intestinal mucosal cells actively transport Tl into the lumen of the GI tract, where it can be reabsorbed (enterohepatic circulation) or eliminated in the feces (30,31). In mammals, Tl excretion via the GI tract is twice that of the kidneys. A small amount of the metal is taken up and excreted in hair; its presence near the roots can be seen microscopically within 3-4 d of intoxication. Thallium has been detected in the milk of poisoned female rats, mice, guinea pigs and humans, and a significant fraction of free plasma Tl crosses the placenta barrier (32). Some of the metal is retained in bone and other tissues (Tl levels increase with time in chronic exposure), which suggests incomplete homeostatic regulation of the metal in the body and accounts for its cumulative toxicity.

MOLECULAR BASIS OF THALLIUM TOXICITY

The toxic effects of Tl have been demonstrated in a wide variety of biological systems, from yeast and bacteria to plants and animals (33-35). Thallium toxicity has been studied extensively in rats, mice, guinea pigs, rabbits, dogs, cats and humans (36-42). In comparing the relative toxicity of heavy metals, Zitko (43) states only methylmercury is more toxic than Tl. Lucky and Venugopal (7) classify Tl as the most toxic cumulative metal cation. Considerable effort has been devoted to better understanding Tl toxicity at the molecular level. The various mechanisms proposed to account for the metal's Tl toxicity are discussed below. While many of these are tenable based on *in vitro* studies or circumstantial evidence, the precise biochemical mechanisms underlying the clinical manifestations of thallotoxicosis are yet to be proven.

Alteration of K-Dependent Processes

Thallium's ability to interfere with a variety of K^+-dependent processes is thought to play a significant role in its toxicity. The chemical similarities between Tl^+ and K^+ explain, in large part, the similar movements exhibited by these 2 ions in cells and tissues. Gehring and Hammond (28) were among the first to propose that Tl^+ and K^+ have common cellular targets and receptor sites associated with biological

activity and toxicity. Various K^+-dependent proteins are known to posses a higher affinity for Tl^+ than for K^+ (44,45). Since Tl^+ alters the activity of these enzymes and membrane transport proteins *in vitro*, they are possible sites of Tl toxicity *in vivo*.

Several studies have explored various Tl-protein interactions. Yeast aldehyde dehydrogenase (YADH) is a critical enzyme in fermentation that catalyzes the NADH-mediated reduction of acetaldehyde to ethanol. At low concentrations, Tl^+ replaces K^+ in the activation of YADH, but at high levels (> 1.0 mM) Tl^+ inhibits it (46).

Pyruvate kinase (PK) is a Mg^{2+}-dependent glycolytic enzyme that catalyzes the transfer of a phosphate group from phosphoenolpyruvate to ADP yielding pyruvate and ATP. It requires K^+ to attain maximum activity. Kaye (47) demonstrated that PK has 50 times greater affinity for Tl^+ than K^+, and that PK is strongly inhibited by Tl^+ at higher concentrations, possibly due to the formation a Tl^+-ADP complex.

Na^+-K^+ ATPase is responsible for the active transport of monovalent cations across plasma and organelle membranes. This electrogenic antiport is critical for osmotic regulation by cells, the generation of the electrochemical potential gradient responsible for the electrical excitability of nerve cells, and in providing free energy (ATP) for the active transport of metabolites (glucose and amino acids) into some cells. At low levels, Tl^+ has been shown to replace K^+ in the

activation of Na^+-K^+ ATPase and to bind the protein with 10-fold higher affinity than K^+ (28,45). However, at high concentrations, Tl^+ competitively inhibits Na^+-K^+ ATPase (48).

Mitochondria have an abundance of Na^+-K^+ ATPase and are particularly susceptible to the effects of Tl (49). Mitochondrial swelling and vacuolization are common electron-microscopic findings in Tl-poisoned neurons (50). Moreover, Tl compromises mitochondrial energy production by inhibiting pyruvate dehydrogenase complex (PDC) and succinate dehydrogenase (SDH) (51). Thus the metal cation blocks the catabolism of carbohydrates and the entry of electrons into the electron transport chain, thereby decreasing ATP generation via oxidative phosphorylation (52). The presence of ketones (acetone, acetoacetate and β-hydroxybutyrate) in the urine and the clinical finding of metabolic acidosis in thallotoxicosis is a consequence of Tl's inhibition of PDC, SDH and other enzymes critical for normal carbohydrate metabolism.

Thallium may also disrupt normal cell metabolism by stimulating enzymes. At low levels, Tl^+ activates other K^+-dependent enzymes, such as phosphatase, homoserine dehydrogenase, vitamin B_{12}-dependent diol dehydrogenase, L-threonine dehydratase, and AMP deaminase (34,43).

Thallium-Sulfhydryl Group Interactions

Thallium's chalcophilic character may contribute to its observed toxicity in animals and humans. Thallium has a high

affinity for natural ligands that contain sulfhydryl (-SH) groups. These groups are structurally important in several classes of enzymes, such as hydrolases, oxidoreductases and transferases (ie flavoenzymes, pyridoxal phosphate-dependent enzymes and thiol proteases). They are functionally important constituents of cofactors involved in many enzyme-catalyzed reactions. For example, PDC and SDH both have dithiol-containing lipoamide prosthetic groups that function in transacetylation of metabolites in their enzyme complexes. Thallium-mediated sulfhydryl inactivation may play an important role in the overall toxicity seen in thallotoxicosis.

Thallium's affinity for -SH groups explains some of the clinical effects seen in Tl poisoning. Keratin is the structural protein of hair, horn, nail and feathers. Two of keratin's important physical properties, insolubility and resistance to stretching, are attributable to its large number of cysteine residues (53). These residues cross-link, forming disulfide bonds between adjacent polypeptide chains. Thallium blocks formation of the disulfide bonds in keratin, which is manifested clinically by alopecia and anomalies in nail growth (Mee's lines) (54,55).

Other Mechanisms of Action

Thallium has been shown to adversely affect protein synthesis. Mammalian ribosomes are strictly dependent on K^+ and Mg^{2+} for normal interaction between ribosomal subunits.

Tl^+ can replace K^+ causing progressive destabilization and irreversible damage to ribosomes, the 60S subunit being particularly affected (56).

Thallium-induced changes at the molecular level produce alterations in normal physiologic processes. Muscle fiber membranes cannot distinguish between Tl^+ and K^+ at low Tl^+ concentrations, but at higher concentrations they are irreversibly damaged (57). Likewise, Tl^+ affects the excitability of myocardial cells, the action potentials in nerve fibers, and neuromuscular transmission in a similar way, but to a greater extent, than K^+.

Interactions between Tl and riboflavin may play a role in the metal's toxicity. Cavanagh (58) has suggested that Tl impairs cell energy metabolism by causing a deficiency of riboflavin and riboflavin-derived cofactors. The observation that Tl salts produce similar pathological effects in nerves, hair, nails and the heart as thiamine deficiency (beriberi) and trivalent arsenic provides circumstantial evidence in support of this theory. Moreover, Tl salts are known to precipitate riboflavin (59); they were once used for this purpose to isolate riboflavin in milk.

Ali et al (60) found that Tl induced alterations in amino acids (glutamic acid, aspartic acid) and neurotransmitters (glutamic acid, dopamine, serotonin) in rat brains exposed acutely or subacutely to the metal ion. Hasan et al (61,62) reported a significant decrease in several enzymes and

neuropathological changes in the hypothalamus and hippocampus after exposure to Tl. Thallium is also known to produce significant increases of lipid peroxidation in the rat brain (63). Its affinity for thiol groups may reduce glutathione levels (64), causing a concomitant increase in membrane-damaging free radicals and peroxides. It is of interest that the antioxidant effect of selenium antagonizes Tl-induced free radical/peroxide generation and counteracts Tl's toxicity *in vivo* (65,66).

The second-messenger cation, calcium (Ca^{2+}), is vital in the regulation of a number of physiologic processes in the cell. Intracellular Ca^{2+} concentration is maintained at a constant low level by the concerted operation of cellular transport and compartmentalization systems. The mitochondria, endoplasmic reticulum and nucleus serve as the principal Ca^{2+} storage sites in the cell, while membrane-bound Ca^{2+} pumps transport the cation out of the cell and into these organelles (67). Several heavy metals are known to cause prolonged elevation of intracellular Ca^{2+}, resulting in Ca^{2+}-induced cytotoxic responses in various tissues (68). Thallium may elevate intracellular Ca^{2+} by 1 or more of the following mechanisms: Inhibiting Na^+-K^+ ATPase and F_o/F_1-ATP synthase; uncoupling oxidation phosphorylation; or disrupting the normal antioxidant processes in the cell.

Many theories have been proposed to account for Tl's toxicity at the molecular level. It is likely that 1 or more

of them are operative in the cell. This area is of great interest and continues to be fertile ground for further clinical and basic research.

CLINICAL TOXICOLOGY

The symptomatology of thallotoxicosis varies with dose, age and acuteness of intoxication. Curiously, children tend to be less sensitive to Tl than adults (69). A dose of greater than 100 mg (1.4 mg Tl/kg body weight) will produce acute toxicity in adult humans; 500-800 mg is often lethal (8). Smaller doses over longer time periods will produce similar, but milder, symptoms as in acute exposures. Chronic poisoning can produce mild to severe effects depending on the severity of exposure.

Gastroenteritis, polyneuropathy, and hair loss are the dominant clinical features of Tl poisoning. A latent period of hours to 1-2 d may follow acute exposure. Abdominal pain, constipation or diarrhea are common initial complaints, but some individuals experience only nausea and vomiting or itching or a vague dull feeling in the extremities. In high-dose exposure cases, neurologic effects may dominate the clinical picture.

Gastrointestinal Tract

Thallium may cause GI disorders regardless of exposure route. Often, nausea and vomiting occur during the 3-4 d period following intoxication, which may be replaced by severe abdominal pain that is relieved by direct pressure. Signs of enteritis or colitis may be observed; ulceration of the mucosal lining of the colon can ensue, producing GI bleeding (70). Depression of intestinal motility and peristalsis may occur due to possible vagus nerve involvement, resulting in severe constipation.

Nervous System

Neurologic symptoms usually appear in 2-5 d in acute exposure cases, which are characterized by a painful, rapidly progressive peripheral neuropathy that dominates clinically in the second or third week. Sensory disturbances include pain and paresthesias of the lower limbs, numbness in the fingers and toes, with loss of pin-prick and touch sensation (69). Occasionally, hyperesthesia involving the soles of the feet and tibial region occurs; the mere weight of bed sheets on the lower extremities may cause excruciating pain (71). Motor neuropathy is manifested by weakness which is always distal in distribution. The lower body extremities are primarily affected. Upper extremity involvement occurs infrequently and cranial nerve participation is rare. Insomnia, headache, emotional lability (lamentation with a theatrical or hysteri-

cal effect), anxiety, tremor, ataxia, choreoathetosis, and signs of cranial nerve involvement (ptosis, nystagmus, abnormal palatal or vocal cord movements) may develop. Psychosis with paranoia, depression, aggressiveness and hallucinations are not uncommon. In chronic Tl poisoning, ataxia and paresthesia may be the outstanding symptoms. In time, the paresthesia may progress to frank peripheral neuropathy with weakness and atrophy of the associated musculature.

Eye

Retrobulbar neuritis with reduction of vision and central scotoma may occur as a result of Tl intoxication (72). Cataracts, iritis, inflammation of the eyelids, and intraocular hemorrhage have been reported in animals (73). Subnormal or absent retinal electrogenesis may be observed as soon as 2 d post-intoxication, as measured by electroretinography (74).

Skin

Alopecia is the best known effect of chronic Tl poisoning. Epilation begins about 10 d after ingestion; complete hair loss is seen in about 1 mo. This long latent period coincides with the maturation period of the new epithelial cells of the hair papilla, which Tl targets. After a maturation period of 10-14 d, hair loss is evident. Axillary and facial hair, including the inner 1/3 of the eyebrows is

usually spared, which has been attributed to Tl-induced lesions to the sympathetic nervous system (2). However, most evidence supports direct involvement of Tl with the hair follicles as the mechanism of toxicity (54,75,76). Thyresson (54) found a high ^{204}Tl content in active hair follicles, whereas resting follicle uptake of the nuclide was low. Hair loss is usually reversible, but severe poisoning may lead to permanent alopecia. Thallium deposits in hair samples can be observed microscopically as regions of dark brown or black pigmentation near the hair roots 3-5 d post-intoxication. Other observed dermatological effects may include palmar erythema, acne, anhydrosis, and dry scaly skin, which is caused by the metal's toxic effect on sweat and sebaceous glands. Dystrophy of the nails, seen as the appearance of white semilunar bands (Mee's lines), appear 3-4 w after intoxication.

Heart

Cardiac signs, such as sinus tachycardia, irregular pulse, hypertension, and angina-like pain, have been reported during the second week after exposure. While some investigators attribute these signs to vagus nerve involvement, others have noted electrocardiographic changes (nonspecific ST segment abnormalities, flattened or inverted T-wave) that suggest direct myocardial damage (72).

Kidneys

Renal function is usually not grossly impaired, despite the fact that the kidneys accumulate the highest concentration of Tl of any organ. Albuminuria, hematuria, elevated blood urea nitrogen (BUN) or decreased creatinine clearance indicate renal involvement, whereas coproporhyrinuria and uroporphyrinuria reflect liver and muscle damage (71,77). A definitive diagnosis of thallotoxicosis is based on the demonstration of above-normal Tl levels in the urine or other biological specimens.

Reproductive System

Experimental evidence suggests that the reproductive system is highly susceptible to Tl. Decreased libido and impotence in humans, and lower sexual activity in laboratory animals was noted with chronic exposure to the metal. In animals and humans, the testis accumulated high levels of Tl. Moreover, morphological and biochemical changes in the testes and decreased epididymal sperm motility were noted in rats exposed to 10 ppm Tl in drinking water of 2 mo (78). In experiments on embryonic mouse cultures exposed to 1 μM Tl, only 14% of embryos reached the blastocyst stage of development (79). The human fetus may suffer from transplacental exposure to Tl, as evidenced by skin and nail dystrophy, alopecia and low body weights in newborns of Tl-intoxicated mothers (80).

Teratogenicity and Carcinogenicity

Thallium is teratogenic in chick embryos, causing achondroplasia, leg bone curvature, parrot-beak deformity, microcephaly and decreased fetal size (81). However, teratological investigations in mammals have produced conflicting results (82,83).

Large doses (3 mg/kg $TlCl_3$) of the trivalent Tl cation inhibited tumor growth in Sprague-Dawley rats carrying an ascitic form of Walker 256 carcinoma (84). However, it had no effect on L1210 leukemia cells or other types of solid tumors. Buschke and Peiser (85) found that chronically-exposed rats developed gastric papillomas and inflammatory proliferative lesions in the forestomach, such as hyperkeratosis and epithelial cysts and tufts that extended into the muscularis mucosa. Thallium induced single-stranded DNA breaks in C_{57} B/6 mouse cell cultures, and its mutagenic activity, as measured by dominant lethal testing, was higher than that of mercury chloride (86).

LABORATORY EVALUATIONS

Analysis of urine, feces, hair or saliva for Tl contents should be done to assess the extent of Tl exposure and to monitor treatment. Although a variety of analytical methods can be employed in the determination of Tl, atomic absorption spectroscopy (AAS) is the method of choice in most clinical

laboratories.

Estimates of Tl concentrations in the normal population are 7-15 ng Tl/g hair and ~0.3 µg Tl/L urine. Salivary levels of the metal are ~15 times higher than urinary levels, and thus may serve as a measure of Tl toxicity in people with severe constipation, renal failure or other conditions that prevent collection of standard biological materials (30).

Other laboratory findings in Tl poisoning are nonspecific. Anemia and hemolytic changes are occasionally reported, but the lymphocytosis and eosinophilia sometimes seen are likely due to secondary infection. Elevated liver enzymes may be found, although the metal is not particularly hepatotoxic. Hypokalemia and hypochloremic metabolic acidosis have been observed (2,71). Coproporphyrinuria and uroporphyrinuria may be seen, which may reflect liver and muscle damage (69). Decreased creatinine clearance, elevated BUN, and proteinuria indicate renal function impairment. A slightly elevated cerebrospinal fluid protein level may occasionally be seen, but rarely is it greater than 100 mg% (69).

DIAGNOSIS

The diagnosis of thallotoxicosis is often difficult unless the etiology is well known. The triad of gastroenteritis, peripheral neuropathy of unknown origin, and alopecia should alert the clinician to the possibility of Tl poisoning.

Unfortunately, the diagnosis of Tl poisoning often occurs only after hair loss is observed (3-4 w post-intoxication), thus diminishing the effectiveness of treatment and increasing the likelihood of permanent residual effects. It must be stressed that hair loss does not always occur (70,72,87). Thallium poisoning should be considered any time the patient presents with neurological symptoms of unknown etiology, particularly peripheral neuropathy.

The occurrence of nonspecific symptoms may lead to misdiagnosis, particularly in chronic Tl intoxication. Thallium-induced motor neuropathy must be differentiated from that seen in acute intermittent porphyria or Guillian-Barre' syndrome. Erythema, renal impairment, fever and hair loss may suggest systemic lupus erythematosus, particularly in young females (88).

Routine metal screening tests often are not designed to detect Tl. A Tl mobilization test can be used to confirm poisoning; this entails giving 45 mEq potassium (K) po, then collecting and analyzing urinary excretions during the subsequent 24-h period (89). Care should be taken to insure that urine specimens are collected in a non-metal container and then rapidly acidified to prevent surface adsorption or coprecipitation with other urine constituents. AAS is preferable to colorimetric or spectrophotometric methods because of its high specificity for Tl and its low detection limits (~3 ppm, flame AAS; <1 ppb, graphite furnace AAS) (90).

Additionally, a qualitative test for Tl can be done by microscopically examining hair roots for Tl deposits (black or dark brown pigmentation). In poisoned patients Tl deposits can be found in 95% of scalp hair examined, 50-60% of chest/leg hair, and 30% of eyebrow/eyelid hair (91).

TREATMENT

Estimation of the dose, time elapsed since exposure, and physical status of the patient will aid in determining whether induced vomiting, gastric lavage, supportive care or specific therapy is required, and the priority of these management steps.

In recent acute exposure, ipecac syrup should be given or lavage performed to remove as much Tl as possible from the GI tract. Symptomatic and supportive treatment should be begin immediately, with special attention given to the patient's respiratory and circulatory status.

The treatment objective in Tl poisoning is to enhance the metal's elimination from the body. This is accomplished by inhibiting absorption/reabsorption of the metal from the digestive tract and by mobilizing the Tl from tissue storage sites without exacerbating the patient's symptoms.

Attempts to mobilize Tl by use of chelating agents have yielded negative or marginal results. Ethylenediaminetetra-acetic acid and diethylenetriaminepentaacetic acid are

completely ineffective (92,93). Dimercaprol (British anti-Lewisite, BAL) and D-penicillamine failed to enhance Tl excretion in experimental animals (94,95). Dithiocarb (sodium diethyldithiocarbamate, NDDC) chelates Tl *in vivo* and enhances renal excretion, but the lipophilic metal-ligand complex promotes Tl redistribution to the brain, thus exacerbating neurologic symptoms (96). Treatment with dithizone (diphenyl-dithiocarbazone) yielded equivocal results (97,98) and was found to be goitrogenic and diabetogenic in animal studies.

Potassium increases the urinary excretion of Tl (97) and increases the LD_{50} of Tl in rats (28). Two possible mechanisms are responsible for increased thalluresis: K blocks tubular reabsorption of Tl, or K mobilizes Tl from intracellular stores thereby raising plasma levels and increasing its availability for filtration by the kidneys. But like NDDC, K may also cause dangerous redistribution of Tl to the central nervous system (99), and thus should be used with caution.

Given orally, prussian blue (potassium ferric hexacyano-ferrate(II), PB) absorbs monovalent Tl cations in its crystal lattice, thereby interrupting its enterohepatic circulation. Prussian blue and the Tl-PB complex are not absorbed from the GI tract and are eliminated in the feces. About 7% of PB is degraded to cyanoferrate, which is absorbed and rapidly eliminated in the urine, carrying some bound Tl with it in the process. Prussian blue has a high therapeutic index and is, for all practical purposes, nontoxic (100). It is most

effective when administered within the first 48 h after ingestion, but results from human studies suggest PB has therapeutic utility throughout acute and chronic intoxications.

Prussian blue exists in 2 forms, the so-called insoluble form and the colloidal (soluble) form; the latter form absorbs more Tl. Stevens (101) compared the effectiveness of PB in human trials and found it to enhance fecal elimination of Tl. Since Tl may cause severe constipation, 250 mg PB/kg/d in 4 divided doses should be given in a 15% mannitol solution (50 ml). Prussian blue is not commercially available in the US, but can be obtained from Heyl Chemisch-Pharmazentische Fabrik Gmbh & Co (Berlin). Prussian blue is not yet approved for human use by the FDA. Activated charcoal may be used instead of PB, but it is not as effective (100). The recommended dose of activated charcoal is 500 mg/kg/d, given twice daily.

Forced diuresis enhances the elimination of Tl (102) and may be useful in acute intoxication. Hemodialysis, however, is of little benefit once Tl has been sequestered intracellularly unless potassium is given concurrently. For this reason, hemodialysis is only indicated in the initial stages of acute intoxication when Tl plasma levels are relatively high or in the case of renal severe insufficiency/failure (103). Hemofiltration was found ineffective in eliminating Tl (103).

The decorporation of several heavy metals is enhanced by

the concurrent use of 2 or more chelators. In acute Tl-exposed laboratory animals, a chelator-PB combination was shown to produce a synergistic effect that enhanced the overall elimination of the metal from the body. Rios et al (104) demonstrated that the combined administration of D-penicillamine and PB reduced the Tl content in rat target organs more than single administrations of these antidotes, without promoting dangerous redistribution of Tl to brain. The use of chelator-PB combinations to treat thallotoxicosis deserves more research attention.

In summary, acute thallotoxicosis should be treated by gastric lavage/emesis if ingestion was recent, followed by oral PB and laxatives and forced diuresis with K loading. If plasma Tl levels are elevated or if the patient is in renal failure, hemodialysis should be considered.

PROGNOSIS

Thallotoxicosis is a serious illness with high morbidity and mortality whose outcome is hard to estimate. In general, cases with a fulminating onset are rapidly fatal. The longer the patient survives, the better the prognosis for survival, although long-lasting or permanent neurologic sequelae may result. In a follow-up study conducted 4 y after Tl intoxication, Reed (2) found a 58% incidence of chronic neurologic defects involving both the peripheral and central nervous

systems in surviving patients. Severe and presumably permanent deterioration in intellectual function (memory and performance abilities) has been documented in at least 1 case (105). However, if Tl poisoning is recognized and treated early, the chance for full recovery is good.

CONCLUSIONS

Thallium poisoning is a complex and often fatal affliction involving a wide range of organs and tissues. Because of its similarity to potassium, Tl follows K distribution pathways and inhibits a number of K-dependent processes. Several mechanisms have been postulated to account for Tl's toxicity, including ligand formation with sulfhydryl groups of enzymes and transport proteins, inhibition of cellular respiration, interaction with riboflavin and riboflavin-based cofactors, alteration of the activity of K^+-dependent proteins, and disruption of intracellular calcium homeostasis. The clinical triad of gastroenteritis, peripheral neuropathy of unknown etiology, and alopecia should alert clinicians to the possibility of Tl poisoning. The diagnosis of thallotoxicosis is confirmed by finding elevated Tl concentrations in urine or other biologic materials. Treatment should consist of gastric lavage/emesis to reduce exposure to the metal, PB (or activated charcoal) and laxatives to enhance fecal elimination, and forced diuresis with K loading to increase

renal clearance. If K is given, the patient's status must be monitored carefully because neurologic and cardiovascular symptoms may be exacerbated. Hemodialysis may be useful at the outset if plasma Tl levels are high or in the case of renal failure. A favorable prognosis is justified if the poisoning is recognized and treated early. The longer the exposure to Tl, the greater the risk of permanent neurologic abnormalities.

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TABLE 1. TOXICITY OF THALLIUM SALTS.

COMPOUND	ANIMAL	ROUTE DOSE[1]	TOXIC (mg Tl/kg)	DOSE	REF
Tl Acetate	rat	ip	LD_{50}	23	106
		po	LD_{50}	32	
	rabbit	iv	LD_{Lo}	20	
		ip	LD_{Lo}	13	
	guinnea pig	ip	LD_{Lo}	7	
		po	LD_{Lo}	12	
	dog	po	LD_{Lo}	20	
Tl Oxide	rat	ip	LD_{50}	72	
		po	LD_{50}	39	
	rabbit	iv	LD_{Lo}	39	
		ip	LD_{Lo}	60	
	guinnea pig	ip	LD_{Lo}	30	
		po	LD_{Lo}	5	
	dog	po	LD_{Lo}	30	
Tl Nitrate	rat	sc	LD_{Lo}	20	34
	mouse	po	LD_{50}	32.5	
	dog	po	LD_{Lo}	45	
Tl Sulfate	rat	po	LD_{50}	15.8	
	mouse	po	LD_{50}	29	
	human	po	LD_{Lo}	8	69

[1] LD_{Lo} is the lowest dose producing lethality during 14 d observation period.

TABLE 2. THE PHYSICAL PROPERTIES OF THALLIUM. (Adapted from Trump DM: The Integral Scientist, Assoc of Shareware Professionals, 1991)

Atomic number	81
Atomic weight	204.3833
Density (g/cm^3 at 20 °C)	11.85
Melting Point (°C)	303.55
Boiling Point (°C)	1456.85
Crystal Structure	
Hexagonal close packed	<230 °C
Body centered cubic	230 - 303.55 °C
Molar Enthalpy of	
Atomization	182.845
Fusion	4.31
Vaporization	166.1
Electron shells	$[Xe]4f^{14}5d^{10}6s^26p$
Oxidation states	+1 +3
Atomic radius (pm)	171.0
Ionic radii (pm)	
Tl^+	150.0
Tl^{3+}	88.5
Molar Ionization Energy (kJ/mol)	
I	589.3
II	1971.0
III	2877.0
Pauling's electronegativity	1.8

CHAPTER 2

QUANTITATIVE ANALYSIS OF TRACE LEVELS OF THALLIUM IN BIOLOGIC MATERIALS BY ATOMIC ABSORPTION SPECTROSCOPY

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ABSTRACT

Thallium is a highly toxic metal (LD_{50} 8-12 mg/kg, man; LD_{50} 30 mg/kg, rat) normally present at trace levels in the environment except when concentrated by human activities. The need for a rapid, specific and sensitive analytical method for thallium determination in the clinical laboratory is met by atomic absorption spectroscopy (AAS). Basic AAS principles and instrumentation are discussed. Sample preparation techniques for trace metal analysis of biological material are presented; the destruction of organic matter and liquid-liquid separations are emphasized. The application of flame AAS and graphite furnace (electrothermal) AAS to the determination of thallium in biologic materials is reviewed.

KEYWORDS: Thallium; flame AAS; graphite furnace AAS; electrothermal AAS; chelate; wet ashing; sodium diethyldithiocarbamic acid; methylisobutylketone.

THALLIUM

The toxicity of thallium and its salts has been known almost since the element's discovery in 1861 by Crookes. Named for the brilliant green spectral line it produces, thallium is recognized as one of the most toxic heavy metals (LD_{50} 8-12 mg/kg, man; LD_{50} 30 mg/kg, rat) (1,2).

Normal Thallium Levels

The crustal abundance of thallium is 0.3 ppm, with higher levels found in granite, shale and manganese nodules (Table 1). Natural thallium concentrations in seawater and freshwater are estimated to be <0.03 ppb (3). Normal thallium levels in humans and animals are <1 ppb in blood and urine and <10 ppb in tissues (4,5).

Production and Uses

Thallium is found in pyrites used to make sulfuric acid; the H_2SO_4 production process generates waste residue that yields commercially recoverable levels of the element. Thallium is concentrated in iron, lead, cadmium and copper smelters as flue dust which is further processed to recover commercial quantities of the metal. Annual worldwide thallium production is only ~5 tons (6); recent US production is estimated to be 1500 lbs. Thallium is also released to the environment by cement plant emissions and through agricultural

use of phosphate fertilizer.

A small amount of thallium is used in alloys (anticorrosive), optical lenses (increases refractive index), low-temperature thermometers, dye and pigments (artist paints), semiconductors and ceramics, vapor lamps, scintillation counters, portable radiation (γ ray) detection devices, and in organic chemistry (catalyst).

Mining and smelting, together with sulfuric acid production and coal-burning power plants, are the major iatrogenic sources of thallium in the environment. Major non-point sources are auto emissions (urban) and phosphate fertilizer (rural) but their contribution to the total environmental burden of the metal has not been fully assessed. The use of thallium in these commercial applications gives rise to concerns about occupational exposure and environmental pollution.

Thallium sulfate (Tl_2SO_4), an odorless and tasteless compound, was once used in the US as an insecticide/rodenticide, but was prohibited 1975 as a consequence of several highly publicized accidental, criminal and suicidal poisonings. Many developed countries have banned or strictly controlled its use for this purpose. However, its continued use in developing countries has resulted in a number of accidental human and animal poisonings (7-9).

Thallium was once used to treat syphilis, gonorrhea, tuberculosis, ringworm infestation of the scalp, and as a

cosmetic epilant. Safer and more efficacious drugs long ago replaced thallium in the treatment of these conditions. The only medical use of thallium today is as a radioactive contrast agent (^{201}Tl) to image tumors and to visualize the heart in myocardial function tests (10,11).

Absorption, Distribution, Excretion

After rapid and complete absorption from the respiratory or gastrointestinal tract or skin, water-soluble thallium salts are widely distributed to organs and tissues, including the brain, heart, kidney, skeletal muscle and testis, the principal targets of thallium toxicity (12). Since Tl^+ (1.50 Å) and K^+ (1.38 Å) are univalent ions with similar ionic radii, Tl^+ interferes with (Na^+-K^+) ATPase (and other K^+-dependent enzymes) and mimics K^+ in its movement and intracellular accumulation in mammals (13). Tl^+ is less rapidly released than K^+ once it moves into the cell. Its half-life in rats is estimated to be 4 d (14). Thallium is excreted by the kidney into the urine and is also actively transported by intestinal mucosal cells into the lumen of the gastrointestinal (GI) tract where it can either be reabsorbed (enterohepatic circulation) or excreted in the feces. A small amount of the metal is taken up and excreted in the hair, and its presence near the roots can be seen microscopically within 3-4 d of intoxication. Some thallium is retained in bone and other tissues (Tl levels increase with time in chronic

exposure), which suggests incomplete homeostatic regulation of the metal in the body and accounts for its cumulative toxicity.

Toxicity

The toxic effects of thallium in man and animals have been extensively studied and have been the subject of several reviews (15-17). Acute thallotoxicosis produces a complex clinical picture due to its multiorgan involvement. The predominant symptoms in acute exposure result from the metal's effect on the GI tract, peripheral and central nervous system, cardiovascular system, kidney and skin (Table 2). Subacute and chronic thallotoxicosis may occur in the general population (ie, accidental/intentional food poisoning) or in thallium-exposed workers. Symptoms of subacute and chronic thallium intoxication are similar to acute intoxication, but are less pronounced (Table 3). The symptoms in long-term low-level exposure (ie, industrial emissions and runoff) are poorly understood, but may include partial alopecia and mild neurological disturbances. In humans, maternal exposure produces detectable thallium levels in amniotic fluid and breast milk. Thallium is teratogenic in chick embryos but equivocal effects were observed in rats, mice and cats (18). Thallium may cause deformities in humans if the fetus is exposed during the first trimester (19). It has marked antimitotic activity in rapidly dividing tissues, such as hair

follicles and the testes (15).

ATOMIC ABSORPTION SPECTROSCOPY (AAS)

Many analytical methods have been applied to the determination of thallium in biological materials. Electrochemical methods, such as polarography and anodic stripping voltametry, are sensitive and precise techniques but require significant time and effort in the pretreatment stage to reduce interfering substances in the sample. Neutron activation analysis, isotope dilution mass spectrometry, x-ray fluorescence and inductively coupled plasma mass spectrometry are sensitive specialized techniques not generally suitable for routine thallium analysis in the clinical laboratory setting. Colorimetric methods are relatively insensitive and do not attain the detection limits necessary to determine thallium in chronic exposure cases. Significant improvements in AAS instrumentation and development of many AAS procedures for trace metal analysis have occurred over the past two decades. Today AAS is the dominant method for trace metal analysis of biologic materials because of its speed, specificity, sensitivity and precision.

Principles and Instrumentation

A discussion of AAS principles and instrumentation is presented for readers unfamiliar with the technique. Several

excellent texts are available that treat the subject in greater detail (20-22).

AAS is based on the principle that ground state atoms of a given element will absorb monochromatic light of a given wavelength proportionate to the number of analyte atoms present in the sample (Fig 1). Metallic elements present in a sample are reduced to their ground state by the process of thermal disassociation in a flame or graphite furnace (GF):

$$MX \xrightarrow{\Delta} MX \xrightarrow{\Delta} M^{\circ} + X^{\circ}$$

solution — salt particle — free ground-state atoms

Absorption spectrometers have components which fulfill 3 basic requirements (Fig 2). Electromagnetic energy from a spectral source, either a hollow cathode lamp (HCL) or electrodeless discharge lamp (EDL), emits the characteristic spectrum of the element of interest (the analyte) which is passed through the flame or GF to a monochromator (normally a diffraction grating) where the resonance line is isolated. Slits are used to allow only a narrow portion of the spectrum containing the resonance line to reach the detector, a photomultiplier tube. The signal is amplified, processed and recorded so that suitable calculations can be made (Fig 3).

The flame itself emits radiation which may interfere with the analyte's resonance line, so single-beam alternating current (a.c.) instruments have a chopper located between the

lamp and the flame. The chopped light produces an alternating current in the detector. The instrument's electronics are designed to amplify only the a.c. signal, thus flame emission is not measured. In double-beam instruments a rotating half-mirror is used that alternately passes the sample beam and reference beam to the detector (Fig 3). The ratio of the two beams is measured electronically and is converted to an analyte absorbance or a concentration reading. Fluctuations in lamp intensity, detector sensitivity and electronic gain give rise to instrumental noise. Since these fluctuations are measured in both beams in the double-beam system they cancel each other out, producing a more stable, precise signal than the single-beam instrument. Of practical significance, the 30-minute warmup period required for source lamp stabilization in the single-beam system is avoided, since fluctuation in lamp intensity is automatically compensated for with the double-beam system arrangement.

Data processing stations, readout devices and other accessories are available for the AAS. Background correction, pulse-nebulization, peak-area integration and fast recorders are useful in the analysis of biological samples. Autosamplers enhance analytical precision and free personnel to perform other laboratory functions (Fig 4). Computerized work stations allow for the automated collection, processing and reporting of data; dedicated software packages provide graphics useful for the development and assessment of new

analytical procedures and on-line statistical analysis of data to facilitate quality control.

Flame AAS

In flame atomization, the sample solution is drawn by a venturi effect into a spray chamber and the sample mist is mixed with a fuel gas (Fig 5). The aerosol then enters the flame where the analyte is desolvated, dissociated and atomized in rapid succession. Only the smallest droplets (≤10 μm) reach the flame so much of the sample is wasted (~90%). Two combinations of oxidant-fuel gases are in common use: The air-acetylene flame (2300° C) will atomize about 35 elements; refractory elements require the hotter nitrous oxide-acetylene flame (2900° C). Pulse-nebulization is useful for small samples (Fig 6). A 20-200 μl aliquot is pipetted into a teflon funnel attached to the nebulizer capillary tube; the analyte produces a sharp transient peak that can be quantified. The advantages of flame AAS over GF AAS are its simple optimization requirements, convenience, speed and precision. Disadvantages are the requirement for large sample volumes (3-5 ml) if pulse-nebulization is not available, inefficient use of sample, and its relative lack of sensitivity compared to GF AAS. Because of its advantages, flame AAS should be used whenever sample size and detection limit (DL) are not limiting factors.

Graphite Furnace AAS (Electrothermal AAS)

The graphite furnace's main functional component is a small, cylindrical graphite tube through which the source beam passes. The sample is injected through a hole located on the top of the tube (Fig 7,8). The GF tube is heated by electrical resistance and can attain a temperature of ~3000° C. The GF has two advantages over flame AAS that make it well suited for the determination of trace elements in biological samples -- it uses small sample volumes (10-50 µl) and it has much lower detection limits for most elements (typically 100-1000 times lower than flame AAS). In the GF mode the GF assembly replaces the burner, and it is controlled by a programmer unit that regulates the furnace as it goes through its dry, char (ash), atomize, clean-out, and cool-off stages. As the AAS cycles through its program the sample solution is desolvated, the volatile organic and inorganic matrix material is vaporized and swept out of the tube, the analyte is atomized and its absorbance measured, any remaining analyte or matrix residue is eliminated, and the water-cooled GF assembly drops the tube to ambient temperature prior to the introduction of the next aliquot of sample. The graphite tube is bathed by a continuous stream of inert gas (usually argon) to prevent its oxidation at high temperature. The GF has several disadvantages -- a laborious program optimization procedure must be done for every analyte/matrix combination, marked background problems must be compensated for (discussed below), severe

interferences are common, carbide formation can occur, memory effects and contamination are common, and longer instrumental times are required (eg, 2-4 min/sample vs 5-10 s/sample for flame AAS).

Background Interference

The analyte sample normally contains a variety of non-analyte constituents (eg, ions, molecules) that are released to the gaseous phase at high temperature. Molecular species, in particular, may absorb at the analyte's resonance line and/or scatter the source beam. If not compensated for, this so-called non-atomic (background) absorption would result in an elevated absorbance reading and an inaccurate analyte determination. Three types of background correction systems (BCS) are available -- the deuterium lamp (continuum) BCS, the Zeeman BCS, and the Smith-Hieftje BCS; newer instruments have one or more BCS as a standard feature. Each BCS works on different principles, but their effect is the same; they measure non-atomic absorption which is electronically subtracted from the total signal so an accurate analyte absorbance is recorded (Fig 9).

Sample Preparation

The amount of sample preparation required for biological fluids depends on the analyte and its concentration, sample type and composition, and on the precision and accuracy

needed. No one procedure is applicable in all cases. Some metals can be determined directly in blood or urine; others must be preconcentrated or have at least a portion of the interfering matrix constituents removed. Many times the presence of organic material precludes analyte determination unless it is first destroyed. This is always the case in the trace metal analysis of tissues and fecal matter. Once the organic matter is destroyed and the analyte is brought into solution, the digest may be directly analyzed if the element of interest is present in sufficiently high concentration. If not, a preconcentration step may be necessary to eliminate remaining interferants and to increase analyte concentration so that a determination can be made.

The risk for sample contamination and analyte loss is particularly high during the preparatory steps. Potential sources of contamination are contaminated reagents and dirty glass/plasticware and laboratory equipment (homogenizers, grinders, desiccators). Analyte losses may arise through analyte volatilization at elevated temperature and by analyte adsorption to the walls of beakers, flasks, test tubes or other labware.

Destruction of Organic Matter

Decomposition procedures generally fall into two classes, dry ashing or wet ashing. Sample decomposition procedures release the analyte from the biological matrix by oxidizing

organic material to volatile molecules (eg, CO_2, H_2O, N_2) leaving the analyte in simple inorganic form suitable for analysis. The destruction method used depends on a number of factors: Analyte volatility; sample matrix composition; and the compatibility of the final digest with the AAS or its suitability for the follow-on sample prepatory step.

Dry ashing is relatively straight forward and simple. An accurately weighed sample (5-10 g) is placed in a platinum, silica or porcelain vessel and heated on a hot plate at moderate temperature until it chars. The vessel and sample are transferred to a cold muffle furnace and the temperature is gradually increased to 450-500° C and held there overnight. If any organic material remains, a small amount of water or dilute nitric acid is added to the sample and the drying process repeated. The ash is then dissolved in a dilute acid solution or other appropriate solvent for introduction to the AAS. The method can not be used for volatile elements like arsenic, mercury, zinc or cadmium; partial losses occur with lead, nickel and thallium. (Note: Many variants of this procedure can be found in the literature.)

Wet ashing destroys organic matter by exposing it to strong oxidizing reagents at moderate temperature. The most commonly used oxidants are concentrated mineral acids (HCl, H_2SO_4 and perchloric acid [$HClO_4$]), which may be used individually or as acid mixtures. The digestion is done in a covered beaker or covered Erlenmeyer flask, or preferably in

a Kjeldahl flask. The wet ash procedure described below is but one of many procedures that can be found in the literature.

An accurately weighed sample of ~5 g is placed in a vessel and HNO_3 (5 ml) is added. The mixture is allowed to stand at room temperature until the initial vigorous reaction subsides. H_2SO_4 (8 ml) is added and the mixture is heated on hot plate until it darkens. With a pasteur pipette, 1-2 ml portions of HNO_3 are added until the mixture remains pale yellow in color (avoid charring). After the mixture cools, $HClO_4$ (2 ml) is added and it is gently boiled until the almost colorless solution gives off white fumes. The mixture is cooled, H_2O (2 ml) is added, and the process is repeated again. The solution is cooled, H_2O (5 ml) is added, and the solution is quantitatively transferred to a suitable volumetric flask and made to volume.

One should always exercise caution when using hot concentrated $HClO_4$. If $HClO_4$ is heated in the presence of carbohydrates or alcohols unstable perchlorate esters will form that can violently and spontaneously explode. Always perform a preliminary digest with HCl or HNO_3 which will completely oxidize carbohydrates and alcohols (23).

Wet ashing is generally preferred to dry ashing because analyte loss due to volatilization and retention on the vessel wall is less likely. Other destruction methods are available and are mentioned but not discussed -- the Parr bomb (a

pressure system), microwave digestion, fusion techniques, and plasma ashing (free radical generation). Several good sources for detailed information on destruction techniques are available (23,24).

Separation and Preconcentration

In trace metal analysis of biological samples it is often necessary to separate the analyte metal from the sample matrix in order to reduce interfering substances and/or to sufficiently concentrate the metal so it can be determined by AAS (Fig 10).

Solvent extraction is a convenient separation technique because often separation and preconcentration can be accomplished in one quick and easy step. A simple batch separation technique (Fig 11) frequently used in AAS procedures consists of the following: A volume (say ~30 ml) of pH-adjusted aqueous solution (eg, urine) containing the metal ion (M^+) of interest is transferred into a separatory funnel; a complexing agent (L^-) is added, the solution is shaken and a ML complex forms; a measured volume (say ~3 ml) of organic solvent is added, the two phases are shaken, and the ML complex is quantitatively extracted into the organic phase; the two phases are allowed to separate and the aqueous phase is discarded. The organic phase is directly aspirated into the flame or injected into the GF. Note that the analyte has been moved to a less complex solution (ie, many interferants are

left in the aqueous phase) and the analyte has been concentrated 10 fold. An additional 2-5 fold sensitivity enhancement is normally obtained by using an organic solvent in flame AAS, which is attributable to its improved operating characteristics in the pre-mix burner and flame.

Sometimes batch separations can not concentrate the metal enough for an AAS determination to be made. More powerful preconcentration methods must be resorted to, such as multiple batch separations or continuous separation techniques. Comprehensive analytical chemistry texts (25, 26) and specialized works (27) cover analytical separations in more detail.

Standardization

AAS is a comparative method which, by definition, requires calibration against known standards in order for accurate quantitative results to be obtained. In all comparative methods there is a mathematical relationship that expresses the measured physical parameter as a function of analyte concentration. In AAS, absorbance is the physical parameter measured.

Spectrophotometric methods obey Beer's Law which states, in AAS terms, that the intensity of a source lamp resonance line passing through a mass of absorbing gas decreases exponentially as the number of ground state analyte atoms

increases arithmetically. Mathematically:

$$A = \log I_o/I = abc$$

where A is absorbance, I_o is incident beam intensity, I is transmitted beam intensity, a is absorptivity, b is the path length, and c is analyte concentration. Since a and b are constants, analyte concentration is linearly related to absorbance which means that a plot of A vs. c results in a straight line calibration curve, at least within a limited concentration range. At higher analyte concentrations the straight line curves downward towards the concentration axis due to loss of efficiency in the absorption process (Fig 12). It should be noted that a perfect linear relationship does not exist for the data points in the linear region because indeterminate errors always occur in AAS. The method of least squares is often used to fit a straight line to the plotted data points (Fig 13).

In practice, the analyst prepares a blank and a series of analyte standards and measures their absorbance. Samples of unknown analyte concentration are similarly measured. Regression analysis of analyte concentration vs. blank-corrected absorbances is calculated, from which the analyte concentration in the samples can be determined. If necessary, samples are diluted to fall within the concentration range of the standards.

AAS standards can be prepared in various ways. The simplest and fastest method is to prepare aqueous standards over the concentration range desired. However, aqueous standards are often unreliable because they do not compensate for matrix and interelement effects, incomplete recoveries and sample contamination. It is better to use standards that have been subjected to the same procedure as the samples.

It is important to match the standard matrix and sample matrix as closely as possible, since often absorbance readings are altered by the presence of non-analyte components (eg, salts, acids, molecules) in the matrix. Matrix matching is difficult to do with complex samples like biological materials. One method of attempting to overcome this problem is to calibrate and analyze within the sample matrix itself by using the standard additions method (SAM). In this procedure an aliquot of sample is analyzed. Known amounts of standard are added to separate aliquots of sample and their absorbances are measured. The increase in absorbance observed is linearly related to the amount of standard added, and a direct comparison is made between the sample absorption and the increased absorption due to the added standard (Fig 14). This relationship takes the form:

$$C = A_o C_{sn} \; / \; (A_n - A_o)$$

where C is unknown analyte concentration in the sample; A_o is

the measured sample absorbance with no standard added; C_{sn} is the total increase in analyte concentration after n additions of standard has been made; and A_n is the absorbance measured after n additions of standard. If C_{sn} vs. A is plotted, a linear relationship is seen; A_o is the y-intercept, and C is found by extrapolating the best fit line back through the x axis.

The SAM must be used with some precaution. Two or more standard additions should be used to insure that absorbance and concentration are linear over the concentration range used. If chemical interferences are observed, they must be constant over the concentration range used. The SAM assumes that the observed absorbance is due only to the analyte being determined. Effective background correction must be verified to insure that erroneously high analyte concentrations are not accepted. A good discussion of SAM calculations and related statistics has been written by Bader (28).

DETERMINATION OF THALLIUM IN BIOLOGIC MATERIALS BY ASS

AAS procedures for the determination of thallium in biological materials have gained widespread acceptance in the clinical laboratory because they are highly specific, sensitive and accurate. Since the flame AAS instrument preceded the GF AAS in development, the early methods for thallium determination were naturally designed for the former. Flame

methods are still applicable in cases of severe acute poisoning and in animal toxicological studies, but they do not have the DLs required to detect chronic thallium exposure (ie, occupational monitoring) or to monitor the treatment of thallotoxicosis. The literature has been reviewed by Subramanian (29,30) and Leloux (31).

Flame AAS Methods

Thallium has a DL of 3 ppm in flame AAS (32), so some type of preconcentration step is necessary in these methods. Early flame AAS procedures were summarized by Zitko (33) and Van Ormer (34).

The Wilson and Hausman method (35) detects microgram quantities of thallium in HNO_3/H_2O_2 digested tissue samples (1-3 g) after neutralizing the digest with NH_3, adding liquid bromine + HBr and heating to expel the excess bromine, and extracting TlBr into 2-octanone. The organic phase is aspirated directly into the flame and absorbance is measured at 377.6 nm. Thallium recoveries of 98.2 ± 1.76% are obtained.

Berman (36) determined thallium in urine, blood and acid-digested tissues by chelation with diethyldithiocarbamate (NDDC) and extraction into methylisobutylketone (MIBK). Prior to chelation/extraction blood samples are treated with 5% trichloroacetic acid (TCA) to remove proteins, urine samples are brought to a pH of 6.0-7.5 with NaOH, and tissue samples

are digested with $HNO_3/HClO_4$ and then similarly pH-adjusted. This method has DL of ~0.5 ppm at a resonance line of 276.8 nm; 95-110% of added thallium was detected in recovery studies. The procedure has been adapted for GF AAS (37).

Savoy et al (38) wet-ashed blood, tissues and feces with a mixture of $H_2SO_4/HNO_3/HClO_4$. Thallium is converted to $TlBr_3$ by addition of bromine water and the metal halide extracted into diethyl ether which is evaporated to dryness. The residue is dissolved in a mixture of dilute acid and aspirated into the flame. DLs of 0.07 ppm (urine) and 0.7 ppm (blood) are claimed at λ=276.8 nm. Nineteen metals/anions were tested for interference at various concentrations, and ≤1% change in absorption by thallium standards was noted. This method is fairly precise; coefficients of variation (CVs) at different concentrations ranged from 3.5 to 6.9%. Thallium levels determined by this method were compared to levels measured by the Christian-Purdy (39) coulometric method, and a 0.98 correlation coefficient was obtained.

Arguably the most frequently used procedure for thallium determination in biological samples by flame AAS is that of Curry et al (40). Tissue and feces are acid digested in a mixture of H_2SO_4/HNO_3. The digest's pH is adjusted between 5.0-6.0 with 2.5N NaOH and the thallium is then chelated with 1% NDDC (1 ml) and extracted into water-saturated MIBK (5 ml) which is then nebulized into the flame. Whole blood (1 ml) is mixed with 5% TCA (1 ml), shaken for 1 h, then centrifuged.

The supernatant is transfered to a suitable container and the precipitate is washed with deionized-distilled water (DI H_2O) (5 ml), stirred and centrifuged again. After the supernatants are combined and the pH is adjusted to 6.0 with 1N NaOH, chelation and extraction are performed as previously stated. Urine (2 ml) is adjusted to pH 6.0 by adding either 5% TCA or 2N NaOH. If a precipitate forms, the mixture is centrifuged and the supernatant transferred to a separate container. The precipitate is washed with DI H_2O (5 ml), stirred and centrifuged. The supernatants are combined and the pH readjusted to 6.0. Chelation and extraction with NDDC and MIBK (2 ml) are performed as above and the organic phase is aspirated into the flame. A DL of 0.04 ppm for MIBK-extracted thallium is obtained vs a DL of 0.2 ppm in aqueous solution. The improved sensitivity is attributed to an increased sample aspiration rate, the formation of smaller sized droplets, and lower flame temperature (decreased analyte ionization). Good thallium recoveries (95-105%) were achieved and the reasonably low CVs obtained (3.5-8.5) indicate the procedure is fairly precise. A modification of this procedure using a tantalum boat decreases DLs to the ppb range, but severe interferences occur which necessitates standardization by SAM.

Wall (41) developed a rapid procedure with sufficient sensitivity for screening urine in cases of suspected thallotoxicosis. Urine samples and aqueous standards are aspirated directly into a 3-slot Boling burner using an air/

acetylene flame. A DL is not reported but ~0.1 ppm at the 276.8 nm resonance line can be inferred. CVs of ≤3% were reported for urine samples spiked with 0.5, 1.0 and 5.0 ppm thallium. The possiblity of matrix interference in urine was investigated but none was found when samples were aspirated directly into the air/acetylene flame.

Graphite Furnace AAS Methods

GF AAS is approximately 100 times more sensitive than standard flame methods for the determination of thallium in biological materials. Until recently, enhanced performance came with a penalty in the form of severe matrix interferences and relatively poor precision compared to flame AAS. This was particularly true for matrices high in chloride (Cl^-) content, like urine. However, the development of commercial GF AAS instruments incorporating Stabilized Temperature Platform Furnace (STPF) (L'vov platform, Zeeman background correction, signal integration, stop-gas during atomization, maximum power heating and matrix modification) (42) technology and powerful data processing stations has gone a long way towards making GF AAS an interference-free technique (30).

Early GF AAS methods for thallium determination used chelation and extraction steps to overcome matrix interferences. Kubasik and Volsin (43) found direct injection of acidified (HNO_3) urine unsatisfactory because background interference could not be reduced to correctable levels using

the deuterium BCS without seriously compromising sensitivity. NDDC and MIBK were used to transfer thallium into a relatively matrix-free environment, but SAM was required for accurate calibration. A sensitivity of 1.5 ppb was achieved using 1.6 µl samples. By using essentially the same method and 20 µl samples, Schaller et al (44) improved the sensitivity to 0.3 ppb.

Chandler and Scott (45) reduced urine matrix interference by using NDDC/toluene to separate thallium after adjusting the aqueous phase to pH 7. The mixed phases form an emulsion that require centrifugation to separate. Calibration is accomplished by using thallium-spiked pooled urine. By using an autosampler to deliver 40 µl samples to a the graphite tube, they achieved good sensitivity (0.1 ppb DL) and excellent precision (3.5% within-batch RSD and 4.4% between-batch RSD). The investigators compared the performance of a standard (uncoated) graphite tube, a pyrolytically coated graphite tube, a L'vov platform in an uncoated graphite tube, and an uncoated graphite tube having an interlay of tantalum foil. The foil-lined tube performed best, enhancing absorbance by a factor of 2, but the tantalum survived only a few firings. Atomization off the wall (uncoated tube) and off the platform (L'vov platform uncoated tube) performed equally well. Interestingly, the uncoated graphite tube performed much better than the pyrolytically coated graphite tube.

Grobenski et al (46) used STPF technology to develop a

direct thallium determination method for the GF AAS. Urine is diluted with 2% HNO_3 and a 10 µl aliquot is injected into the GF. The autosampler then delivers a 10 µl portion of matrix modifier solution composed of 2% ammonium dihydrogen phosphate ($HN_4H_2PO_4$) and 0.02% Triton X-100. The modifier stabilizes thallium and allows a char temperature of 700° C, which removes many interfering matrix consituents thus reducing background absorption to acceptable levels. The authors claim a DL of 0.13 ppb using a 10 µl sample. Pachel and Bailey (47) used a similar approach, but with a matrix modifier solution composed of 4% HNO_3, 10% magnesium nitrate [$Mg(NO_3)_2$] and 0.1% Triton X-100. Urine is diluted 1+1 with the modifier by sequential autosampler injections into the L'vov platform graphite tube. Zeeman background correction is required and matrix matched standards are used for standardization.

Leloux et al (48) developed a direct thallium determination method for urine, blood and feces which was applied in a study of thallotoxicosis in rats. Urine and blood are injected directly into the L'vov platform graphite tube; tissue and fecal samples are dissolved in concentrated HNO_3 at 60-70° C and their supernatants used for the analysis. A matrix modifier solution composed of 1% H_2SO_4, 2% ascorbic acid and 2% Triton X-100 is used to reduce chloride interference and to increase the absorbance signal. The temperature program paramenters used were dry-1 120° C (10 s), dry-2 250° C (20 s), char 800° C (62 s), atomize 1800° C (4.6 s), and

clean-out 2600° C (2 s). DLs of 5 ppb for urine, tissues and feces and 10 ppb for blood are achieved using 4 µl samples + 2 µl modifier. SAM is required for calibration. The authors note that ash buildup in the graphite tube becomes problamatic when blood samples are analyzed which causes memory effects, diminished sensitivity and reduced precision. The authors recommend cleaning the graphite tube periodically by scraping off deposits with a disposable pipet tip. Delves and Shuttler (49) expressed concern over the use of only one standard addition for calibration and suggested that ascorbic acid may contribute to the build-up or residue.

Welz et al (50,51) demonstrated that Cl^- interferes with the GF determination of thallium in two ways -- the metal can prematurely volatilize as TlCl (mp 430° C; bp 720° C (52)) during the char stage of the temperature program and thallium can combine with Cl^- to form TlCl instead of elemental thallium (Tl°) during atomization stage. These researchers used the metal palladium [as $Pd(NO_3)_2$] pre-treated in the GF at 1000° C and 5% hydrogen as chemical modifiers. Palladium works by thermally stabilizing thallium, thereby allowing higher char temperatures which increase the volatilization of Cl^- species. The presence of H_2 in the purge gas enhances the elimination of Cl^- by promoting the formation of volatile HCl. In this method the modifier (10 µl) and undiluted urine (10 µl) are sequentially injected into the GF; more easily prepared acid-matched aqueous standards are used for calibra-

tion since the modifier eliminates all Cl^- interference. With its 2 ppb DL and its apparent freedom from interference, this method appears quite promising for the routine analysis of thallium in the clinical laboratory.

CONCLUSIONS

Thallium is one of the most toxic heavy metals to which animals and humans are exposed. Acute exposure to high levels of thallium produces a complex array of symptoms involving the peripheral and central nervous systems, GI system, cardiovascular system, kidney and skin. The health risk of low-level chronic exposure to humans and animals is not well understood and warrants further investigation. The need for research in this area is underscored by the continued development of new technologies and production processes that use thallium and by periodic reports in the literature of human and animal exposures to the metal (53).

The molecular basis for thallium's toxicity has been largely ascribed to its ability to interfere with K^+-based processes (12). However, there is a growing body of experimental evidence suggesting that other factors may be involved, such as thallium-mediated neurochemical changes (in amino acid and neurotransmitter levels) in the central nervous system (54) and thallium-mediated induction of lipid peroxidation in certain tissues (55). Work directed towards identifying and

characterizing the molecular targets of thallium toxicity should continue.

The dire effects of thallium toxicity were first documented shortly after the element's discovery. Yet, to this date, there remains to be discovered a safe and effective parenteral antidote for thallotoxicosis. More effort should be focused on chelator development and on the clinical evaluation of possible chelator combinations.

Over the past two decades AAS has become the dominant analytical tool for the quantification of thallium levels in biological materials. Acute toxic exposure to thallium can be quickly and easily assessed by flame AAS. Reliable methods are available for the detection of thallium at ppb levels using the GF AAS. The development of direct methods for the determination of thallium (and other metals) that exploit the advantages of Stabilized Temperature Platform Furnace (STPF) technology will undoubtedly improve the clinical laboratory's efficiency and responsiveness to the clinician. The continued development of chemical modifiers is key in this regard.

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TABLE 1. THALLIUM CONTENT (ppm) OF CRUSTAL MATERIAL. Adapted from Fergusson JE (3).

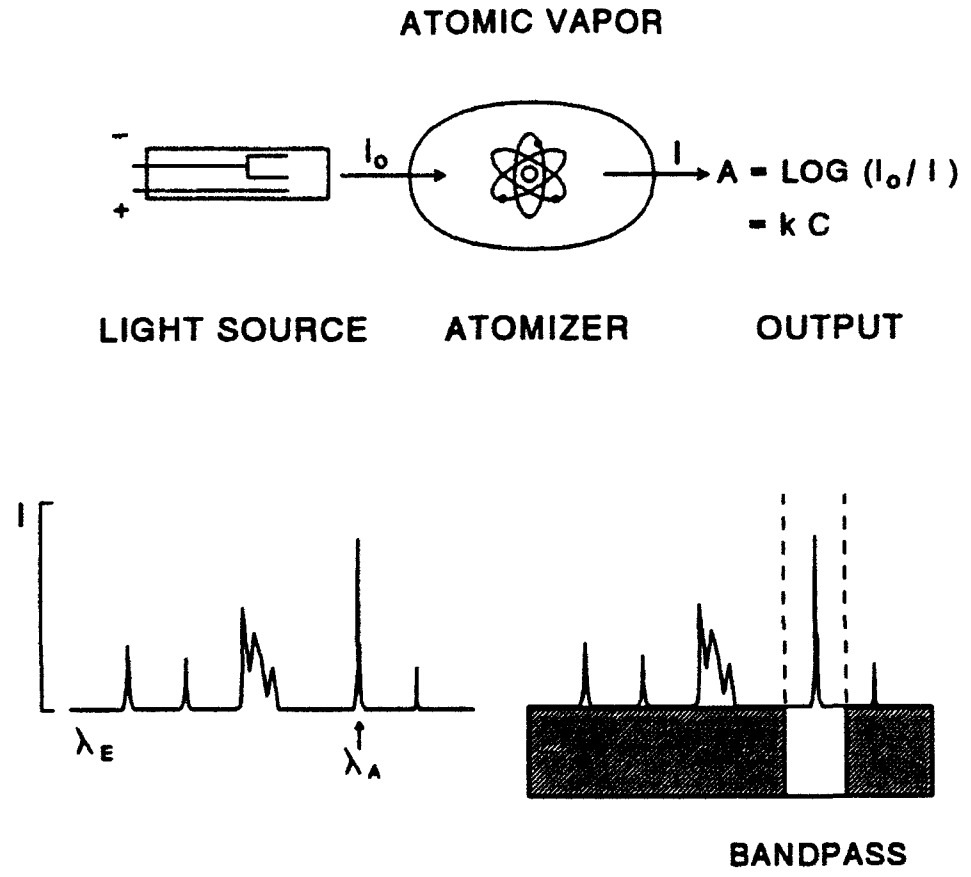
IGNEOUS	(mean)	GRANITE	(mean)	OTHER	
Basalt	0.08	Shale	1.2	Mn nodules	100
Granite	1.1	Limestone	0.14	Phosphate	<0.03-1
		Sandstone	0.36	Coal	0.01-2

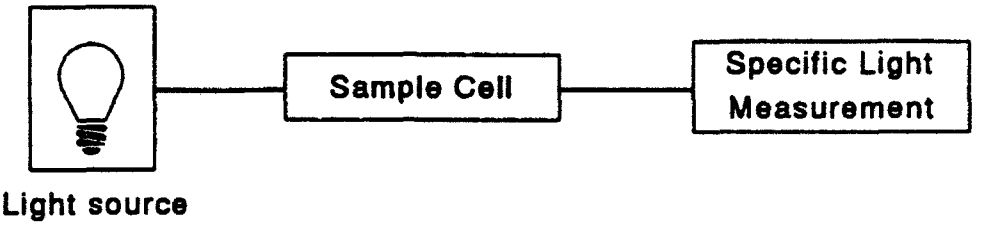
TABLE 2. SYMPTOMS SEEN IN ACUTE THALLOTOXICOSIS

SYSTEM	EARLY EFFECTS	LATE EFFECTS
Gastro-intestinal	constipation loss of appetite nausea & vomiting "brick red" mucous membranes (dog/cat) & tip of tongue (man)	abdominal pain
Nervous	hyperesthesia of soles of feet hyperreflexia excessive thirst sleeplessness psychoses, hallucinations, dementia convulsions, coma	hypoesthesia areflexia (10-15 d) inability to walk
Cardio-vascular	tachycardia moderate increase in blood pressure arrhythmias	
Renal	albuminuria occassionally RBCs, WBCs and casts in urine	
Skin	anhydrosis; dry scaly skin; acne black pigmentation of hair roots	alopecia (10-20 d) semilunar white stripes on nails (Mee's lines)

TABLE 3. SYMPTOMS OF SUBACUTE AND CHRONIC THALLOTOXICOSIS

SYSTEM	SYMPTOMS
Gastro-intestinal	Nausea/vomiting; anorexia; weight loss; stomatitis
Nervous	Paresthesia to definite peripheral polyneuritis (particulary of the lower extremities); ataxia; muscle/joint pain; aptosis; strabismis; facial palsy; mydriasis; psychotic signs (permanent neurological and psychiatric disturbances may occur)
Cardio-vascular	tachycardia, transient EKG changes; arrhythmias
Renal	albuminuria
Skin	delayed alopecia (weeks or months) black pigmentation of hair roots


ATOMIC VAPOR
−
+
I_o
I
A = LOG (I_o/ I)
= k C
LIGHT SOURCE
ATOMIZER
OUTPUT
I
λ_E
λ_A
BANDPASS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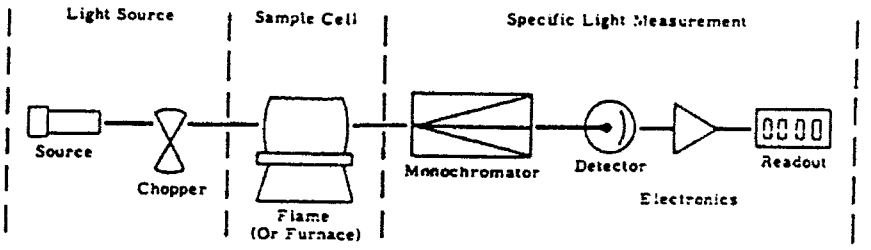
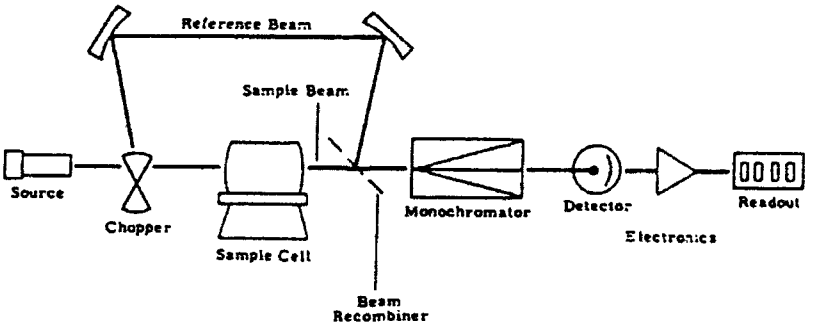
Specific Light
Measurement
Light source


Light Source
Sample Cell
Specific Light Measurement
Source
Chopper
Flame
(Or Furnace)
Monochromator
Detector
Readout
Electronics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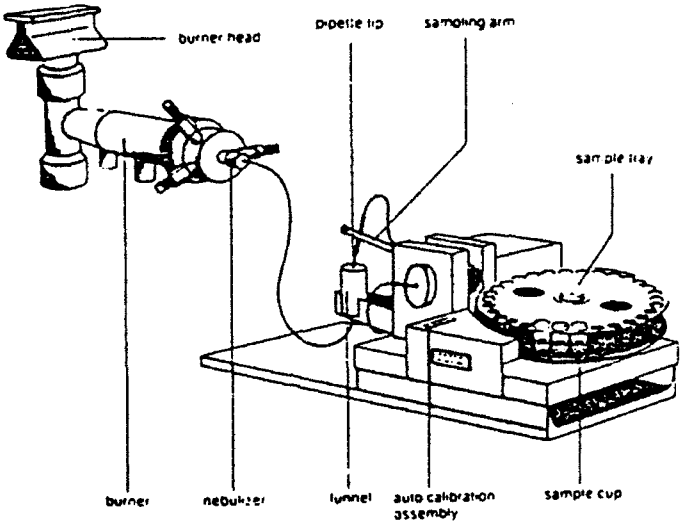
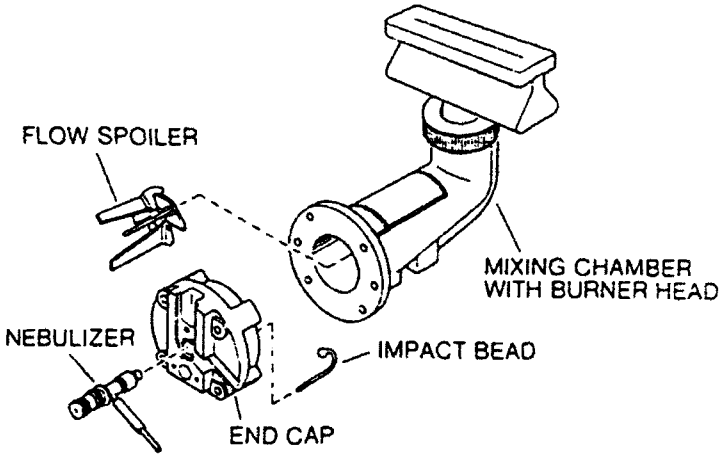
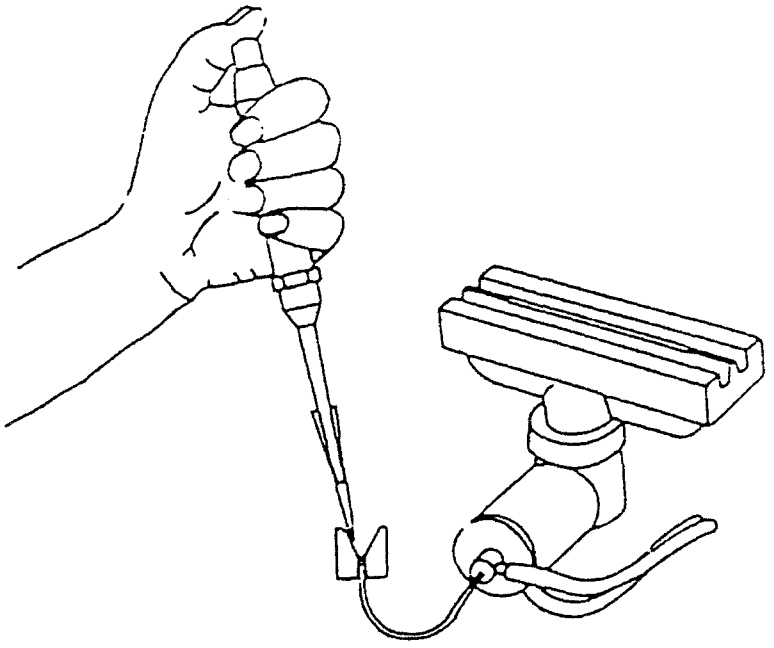
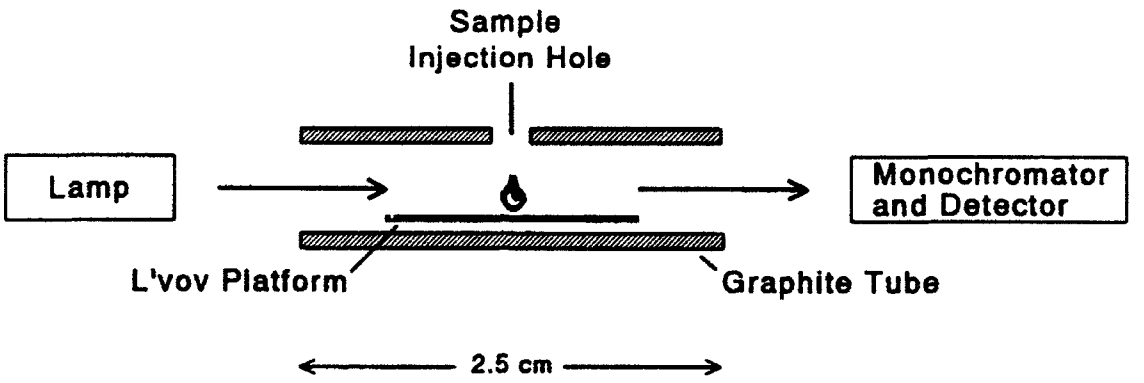
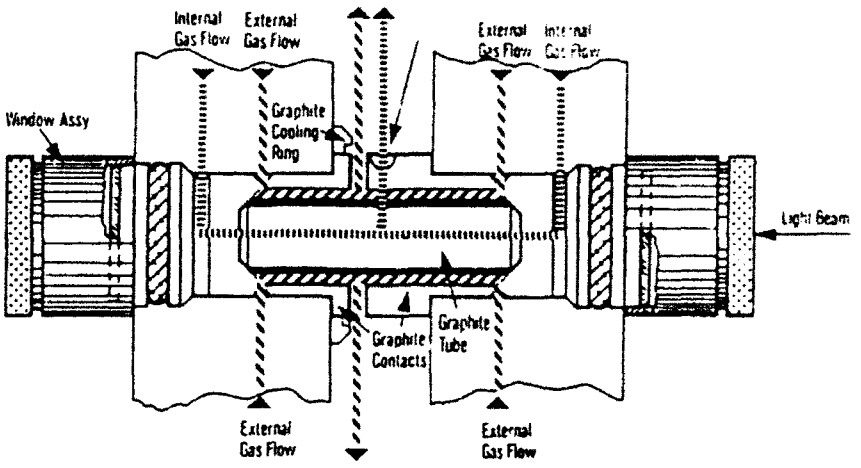
Sample Beam
Source
Chopper
Sample Cell
Monochromator
Detector
Readout
Electronics
Beam
Recombiner

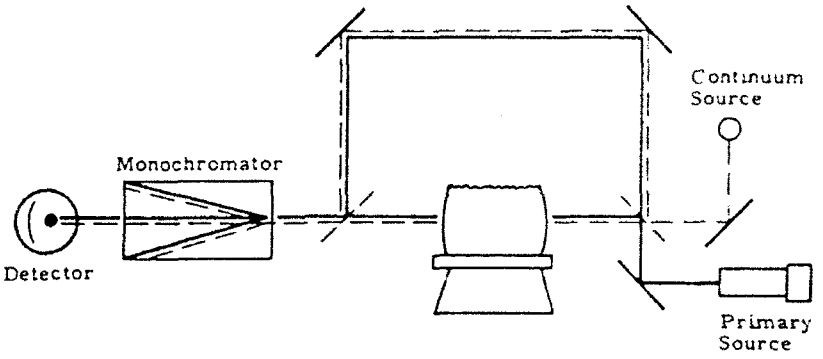

burner head
pipette tip
sampling arm
sample tray
burner
nebulizer
funnel
auto calibration assembly
sample cup

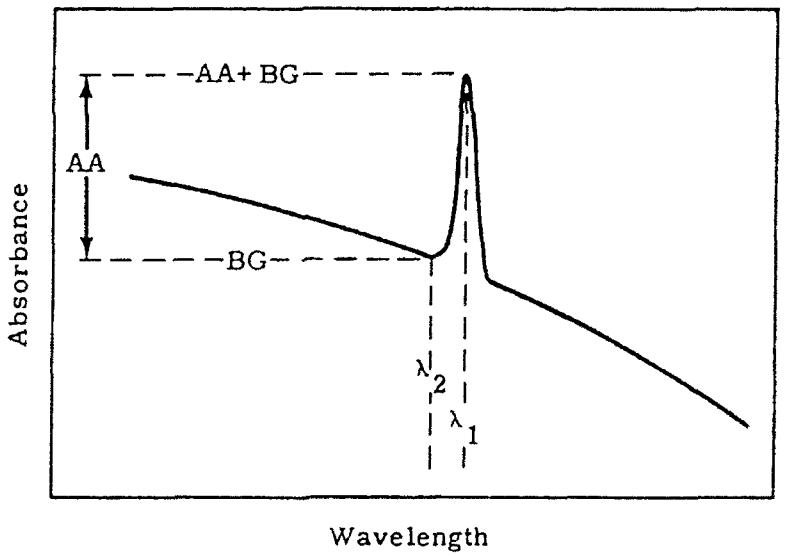

FLOW SPOILER
MIXING CHAMBER
WITH BURNER HEAD
NEBULIZER
IMPACT BEAD
END CAP

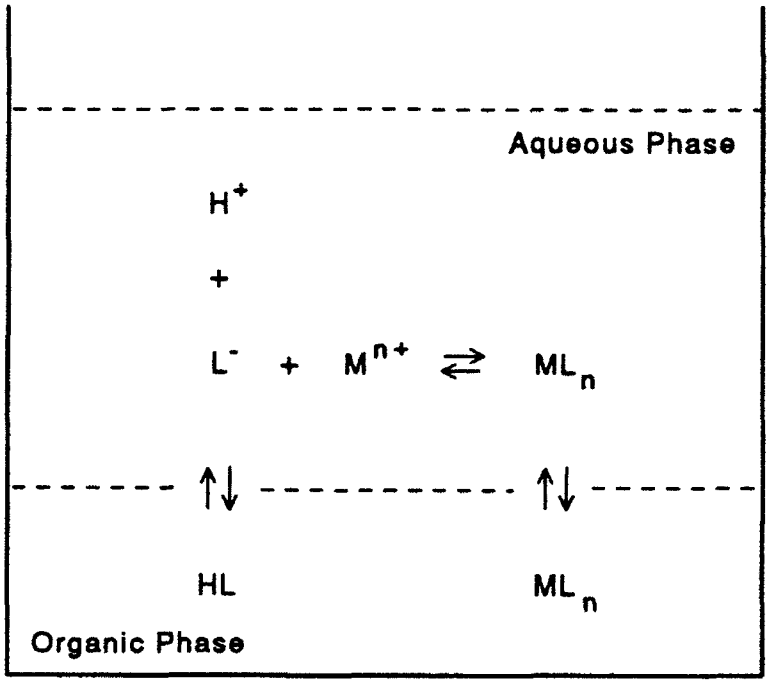


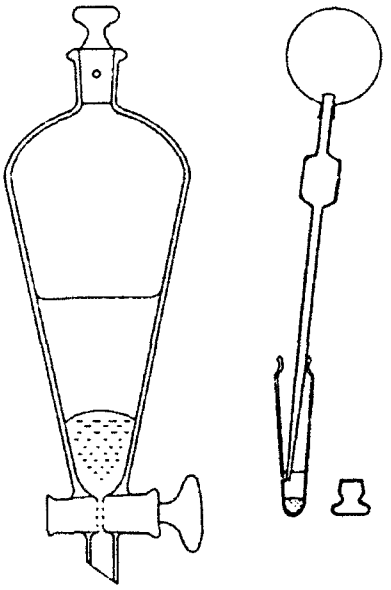

Sample
Injection Hole
Lamp
Monochromator
and Detector
L'vov Platform
Graphite Tube
2.5 cm

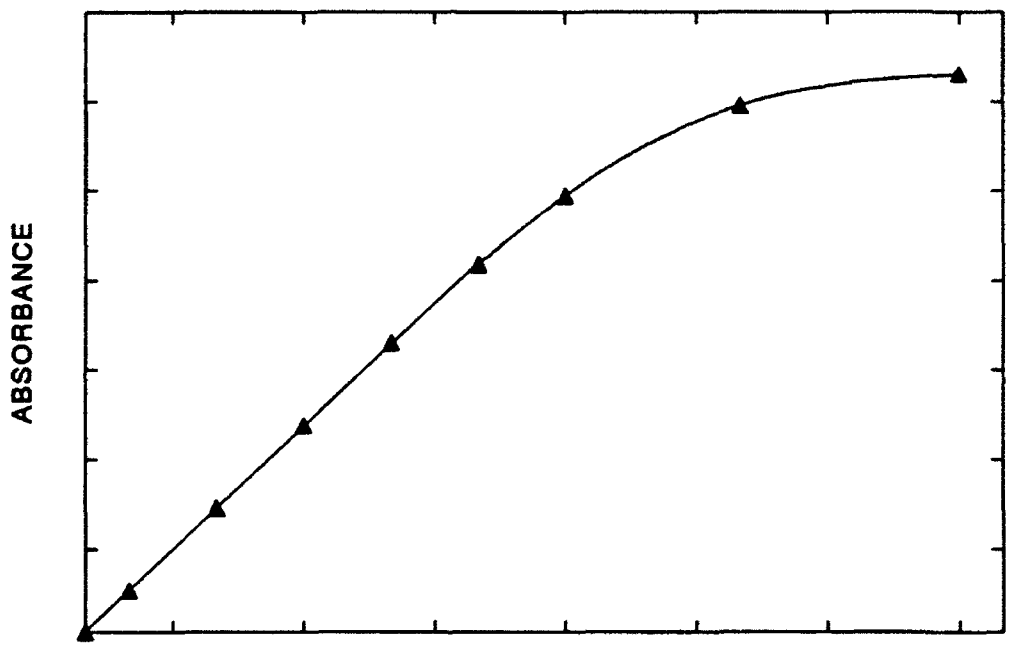

Internal Gas Flow
External Gas Flow
External Gas Flow
Internal Gas Flow
Window Assy
Graphite Cooling Ring
Light Beam
Graphite Contacts
Graphite Tube
External Gas Flow
External Gas Flow

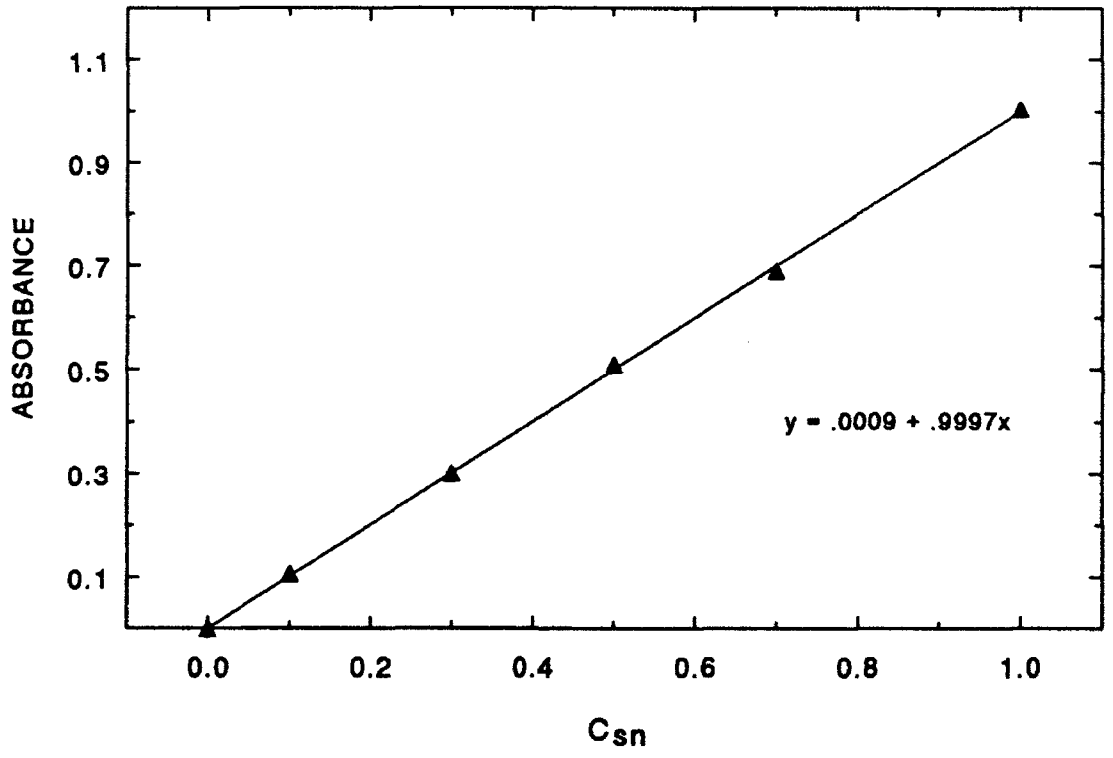

Continuum
Source
Monochromator
Detector
Primary
Source

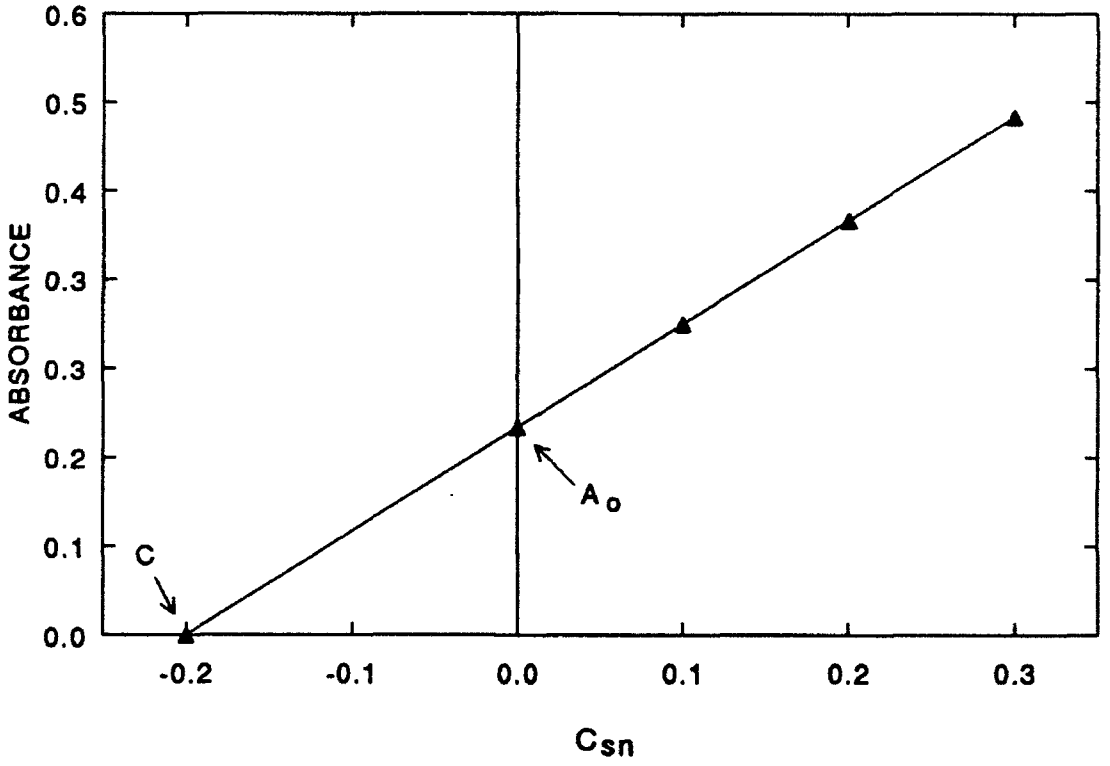

AA+ BG
AA
BG
Absorbance
λ2
λ1
Wavelength


Aqueous Phase
H+
+
L- + Mn+ ⇄ MLn
HL
MLn
Organic Phase




ABSORBANCE
TI CONCENTRATION (ppm)


ABSORBANCE
1.1
0.9
0.7
0.5
0.3
0.1
0.0
0.2
0.4
0.6
0.8
1.0
Csn
y = .0009 + .9997x


0.6
0.5
0.4
0.3
0.3
0.2
0.1
0.0
ABSORBANCE
-0.2
-0.1
0.0
0.1
0.2
0.3
Csn
C
Ao

CAPTIONS

Figure 1. Atomic absorption spectroscopy (AAS) is an analytical technique for quantifying metal (analyte) concentrations in biologic samples, based on the absorption of radiation by free atoms of the analyte of interest. The atomizer heats the sample to create population of free atoms (atomic vapor). The light source emits the spectrum of the analyte of interest. The light beam contains a resonance line (λ_A) of intensity (I_o), that is partially absorbed by free analyte atoms in sample cell (atomizer) to produce a transmitted light beam of intensity (I). A monochromator and a narrow slit-width (bandpass≈2 nm) isolate λ_A from other emitted spectral lines (λ_E). The detector measures radiation intensity, which is converted to an absorbance signal that is proportionate to the analyte concentration in the sample, $A = \log (I_o/I) = k\ C$.

Figure 2. All absorption spectrometers have components that fulfill 3 basic requirements. There must be a light source, a sample cell and a means of specific light measurement. A graphite furnace replaces the flame burner assembly in electrothermal AAS. (From 56, with permission.)

Figure 3. Optical paths for the single beam (top) and double-beam (bottom) systems. (From 56, with permission.)

Figure 4. The Perkin-Elmer AS-3 autosampler. (From 56, with permission.)

Figure 5. Schematic of a pre-mix burner. (From 57, with permission.)

Figure 6. Pulse-nebulization technique. Small sample volumes are injected into a teflon funnel. (From 57, with permission.)

Figure 7. Graphite furnace tube with L'vov platform.

Figure 8. Cross section of the Perkin-Elmer graphite furnace. Inert gas is introduced at both ends of the graphite tube to prevent thermal oxidation of the tube and oxide formation of the free analyte atoms. (From 56, with permission.)

Figure 9. The background correction system uses a continuum source (deuterium lamp) to measure non-atomic absorption (BG), which is subtracted from the combined atomic and non-atomic absorption signal (AA+BG) of the primary source to produce a readout that indicates true atomic absorption (AA=[AA+BG]-BG). (From 56, with permission.)

Figure 10. Extraction of a chelated metal ion into the organic phase. It is assumed that M^{n+} is the predominant form of the metal in aqueous solution and that ML_n is the predominant form in the organic phase.

Figure 11. Apparatus used in batch extraction. A = Separatory funnel, B = Centrifuge tube. (From 27, with permission.)

Figure 12. AAS calibration curve. At higher concentrations, the calibration curve departs from linearity. The most accurate measurements are those falling in the center of the linear portion of the calibration curve, whereas the least accurate measurements are those obtained from the upper part of the curve.

Figure 13. AAS calibration curve. Analyte standards falling in the linear region of the calibration curve are fitted with a calibration line by linear regression. The analyte concentration in the sample is found by rearranging the linear regression equation and solving for $x = [y-b]/m = [y-0.0009]/0.9997$.

Figure 14. Calibration by the standard addition method is used for analyte determinations in complex matrices displaying unpredictable degrees of interference.

CHAPTER 3

A STUDY OF THE ANTIDOTAL EFFICACY OF 2,3-DIMERCAPTO-1-PROPANESULFONIC ACID AND PRUSSIAN BLUE IN THE TREATMENT OF ACUTE THALLOTOXICOSIS IN RATS

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(*Fundam Appl Toxicol*, submitted for publication)

ABSTRACT

A Study of the Antidotal Efficacy of 2,3-Dimercapto-1-propanesulfonic Acid and Prussian Blue in the Treatment of Acute Thallotoxicosis in Rats. Mulkey, J.P. and Oehme, F.W.(1993). *Fundam. Appl. Toxicol.* __,___-___.

Thallium (Tl) is a highly toxic cumulative poison in animals and man. Unithiol (2,3-dimercapto-1-propanesulfonic acid, DMPS) and prussian blue (potassium ferric hexacyano-ferrate(II), PB), given alone and in combination, were evaluated as antidotes in the treatment of acute thallotoxicosis in male Sprauge-Dawley rats. Animals were poisoned with equivalent doses of 20 mg Tl/kg BW po on day 0, using thallous sulfate. On day 1 (24 h later), antidotal treatments began and were continued through day 4 as follows: 50 mg PB/kg BW po, 2/d; 5 mg DMPS/kg BW ip, 6/d (day 1), 4/d (day 2), 2/d (days 3-4); or their combination. Animals were sacrificed by ip injection of sodium phenobarbital 24 h after the last antidotal treatment (day 5) and tissue samples collected. Thallium concentrations in kidney, liver, heart, brain, whole blood and feces were determined by electrothermal atomic absorption spectroscopy. The relative accumulation of Tl in organs was kidney>>heart>liver≈brain. PB induced significant decorporation of Tl from all tissues. DMPS failed to significantly decrease the Tl content in any organ, but significantly

decreased the Tl content in whole blood. PB+DMPS treatment significantly decreased the Tl content in all organs, but to no greater extent than PB alone. PB and PB+DMPS treatments significantly increased the Tl content of feces, whereas DMPS treatment alone produced little effect. This study indicates that PB is a beneficial antidote in the treatment of acute thallotoxicosis in rats. The failure of DMPS to significantly decrease the Tl content in 4 target organs suggests it would not be useful in the treatment of Tl poisoning.

KEYWORDS: Thallium; poison; antidote; chelator; rat; prussian blue; potassium ferric hexacyanoferrate(II); Unithiol; 2,3-dimercapto-1-propanesulfonic acid.

INTRODUCTION

Thallium (Tl) is one of the most toxic heavy metals to animals (LD_{50} ~30 mg/kg, rat) and humans (LD_{50} 8-12 mg/kg) (Downs *et al.*, 1960; Smith and Carson, 1977; Goyer, 1991). Its continued use as a rodenticide in many developing countries accounts for the number of accidental and intentional poisonings reported (Ben-Assa, 1982; Hakala, 1984; Zhou and Lin, 1985; Pai, 1987; Rangel-Guerra *et al.*, 1990). Thallium's unique physico-chemical properties have spurred its increasing use in an expanding number of new technologies such as high-temperature ceramic superconductor materials (Wahlbeck *et al.*, 1991; Betz *et al.*, 1992), thus underscoring concern about exposure risk to animals and humans (Sabbioni *et al.*, 1984; Hapke, 1990).

Water-soluble Tl salts are rapidly and completely absorbed from the respiratory and gastrointestinal (GI) systems or skin, and are widely distributed to organs and tissues, including the brain, heart, kidney, skeletal muscle and testis, Tl's principal target organs (Sabbioni *et al.*, 1980). Because Tl and potassium cations (K^+) share the same charge and similar ionic radii, Tl^+ follows K^+ distribution pathways and alters a number of K-dependent processes (Gehring and Hammond, 1967). Free plasma Tl^+ rapidly moves to the intracellular compartment, as indicated by its short half-life in blood ($t_{½}$=196 min) and large apparent volumes of distribu-

tion (V_{D_β}), *i.e.*, 20 L/kg for plasma and 5-6 L/kg for whole blood (Rauws, 1974; Lameijer and van Zwieten, 1977). The metal is only slowly excreted in feces, urine, hair and secretory products of humans and animals; therefore it is considered a cumulative poison. Possible toxic mechanisms of Tl include ligand formation with protein sulfhydryl (-SH) groups, inhibition of cellular respiration, interaction with riboflavin and riboflavin-based cofactors, and disruption of calcium homeostasis (Mulkey and Oehme, 1993a). The principal clinical features of thallotoxicosis are gastroenteritis, peripheral neuropathy and alopecia. The toxicity of Tl has been the subject of several reviews (Oehme, 1972; Saddique and Peterson, 1983; Manzo and Sabbioni, 1988; Mulkey and Oehme, 1993a).

The treatment objective in Tl poisoning is to enhance the metal's elimination without promoting redistribution to target organs, particularly the brain. To this end, the therapeutic efficacy of different heavy metal chelators has been investigated in attempts to find an effective antidote for thallotoxicosis. Tl^+ is categorized as a soft acid under Pearson's (1968) Hard-Soft-Acid-Base (HSAB) system, and as such tends to form stable metal-ligand (ML) complexes with soft bases such as -SH containing compounds. Thus the ineffectiveness of polyaminocarboxylic acids (e.g., ethylenediaminetetraacetic acid and diethylenetriaminepentaacetic acid) in the treatment of Tl poisoning is not surprising, since these compounds are

considered hard bases (Catsch and Harmuth-Hoene, 1979). Dithiocarb (sodium diethyldithiocarbamate) forms a stable lipophilic complex with Tl^+ *in vitro*, but was found to increase brain Tl concentration (Kamerbeek *et al.*, 1971). Lund (1956) found dithizone (diphenyldithiocarbazone) formed a stable ML complex with Tl^+, thereby increasing the metal's urinary elimination in laboratory animals. But in human trials dithizone produced equivocal results (Chamberlain *et al.*, 1958), and other studies showed it to be diabetogenic and goitrogenic (Kadota and Midorikawa, 1951; Jensen and Kjersulf-Jensen, 1945). Other sulfur-containing compounds, dimercaprol (British anti-Lewisite, BAL), D-penicillamine (PA), and cysteine yielded negative or equivocal results (Catsch and Harmuth-Hoene, 1979).

Potassium (as KCl) enhances urinary excretion of Tl (Gehring and Hammond, 1967; Chamerlain *et al.*, 1958), possibly by displacing Tl from intracellular storage sites; but by raising serum Tl levels, K^+ also increases the risk of Tl redistribution to target organs (Nogué *et al.*, 1982-1983).

The most effective Tl chelator yet discovered is the inorganic dye, prussian blue (potassium ferric hexacyano-ferrate(II), PB) (Stevens *et al.*, 1974). Given orally, this non-absorbable compound adsorbs Tl^+ within its crystal lattice, thereby interrupting the toxic metal's enterohepatic circulation (Rauws, 1974). Found to be essentially non-toxic (Heydlauf, 1969), PB greatly enhances the fecal elimination of

Tl (Thompson, 1981; Lehman and Favari, 1984).

The use of 2 or more antidotes, each using different modes of action to remove toxic metals, has been recognized as a useful therapeutic approach for several years. This so-called synergistic chelate therapy has produced positive results in a number of heavy metal toxicities (Jones, 1983). Recently, Rios and Monroy-Noyola (1992) demonstrated that the combined use of PA and PB in rats provided significantly greater protection against Tl poisoning than PA or PB alone, and suggested that a synergistic interaction between the 2 antidotes may be operative. This finding is surprising because PA is known to promote Tl redistribution to the brain. Additionally, it raises the possibility of finding therapeutic roles for compounds presently considered ineffective when used singly by employing them in synergistic chelate therapy regimens to combat metal toxicity.

The therapeutic effectiveness of the heavy-metal chelator Unithiol (2,3-dimercapto-1-propanesulfonic acid, DMPS), a water-soluble analog of BAL, has been appreciated for more than 30 years in Russia, China and Japan. Compared to BAL, DMPS is chemically stable, much less toxic (LD_{50} 5.02 mmol/kg vs. 0.72 mmol/kg BAL [ip,mice]), and can be given orally (Aaseth, 1983). In Russia DMPS is the antidote of choice for inorganic mercury poisoning. Thallium and inorganic mercury compounds (i.e., mercuric chloride, $HgCl_2$) share similar distribution patterns and target organs in mammals (Aaseth,

1983; Aposhian, 1983) and possess similar physico-chemical properties, as is expected of neighboring elements in the periodic table. Although the therapeutic effectiveness of DMPS has been reported for a number of heavy metals (Aposhian, 1983), including the HSAB soft-acid cations Hg^{2+} and silver (Ag^{+}), we are unaware of any reports concerning the use of DMPS for Tl poisoning.

This study was designed to compare the antidotal efficacy of DMPS to the well-characterized efficacy of PB in acute Tl exposure, and to compare the efficacy of the combined use of DMPS and PB to the single use of these heavy metal antidotes.

MATERIALS AND METHODS

Protocol

A total of 51 male Sprauge-Dawley rats weighing 200-250 g were acclimated for 5 d in the Animal Resource Facility (ARF), Kansas State University, Manhattan, KS. They were housed in a room maintained at a temperature between 22 and 24 °C with a light:dark cycle of 12 h and were fed ARF 3 Lab Chow (Kansas State University Feed Processing Center, Manhattan, KS) and tap water *ad libitum* before and during the study. The animals were randomly assigned to 6 different treatment (T) or non-treatment (NT) groups, fasted for 12 h prior to intoxication, and then dosed by gavage with 24.70 mg Tl_2SO_4/kg BW (20 mg Tl/kg BW) (Fisher Scientific, St. Louis, MO; Lot T-89

784912; FW 504.8) dissolved in deionized-distilled water (DDW).

The rats were allocated to the 6 different groups as follows: 30 animals were placed into 3 T groups (received antidote) of 10 animals each; 21 animals were assigned into 3 NT (received no antidote) groups of 7 animals each. A separate group of 18 rats served as negative controls, receiving no Tl nor antidotal treatment. The PB treatment group (T_{PB}) animals received 50 mg PB/kg BW suspended in 1% Tween-80 (~0.7 ml), twice daily. The DMPS treatment group (T_{DMPS}) rats received 5 mg DMPS/kg BW dissolved in DDW ip (~0.5 ml) 6 times daily on day 1, 4 times daily on day 2, and twice daily on days 3-4. The PB+DMPS treatment group ($T_{PB+DMPS}$) animals received both antidotes in the same doses and by the same routes described above. The 3 NT groups (NT_{PB}, NT_{DMPS}, $NT_{PB+DMPS}$) were given the same volume of suspending vehicle as their T-group counterparts (1% Tween-80, DDW and Tween-80+DDW, respectively). Antidotal treatment began 24 h after dosing with Tl and was maintained for 4 d (Table 1). Body weights were taken daily. The rats were closely monitored for adverse affects after Tl administration and during antidotal treatment.

Sample Collection

The rats were sacrificed by a lethal ip injection of 0.5 ml sodium phenobarbital (Anthony Products, Arcadia, CA; lot

9104) 24 h after the last antidotal treatment (day 5). Blood samples were collected by intracardial puncture using 10 ml plastic syringes and 12-gauge stainless-steel needles, and transferred into heparinized (Elkin-Sinn, Cherry Hill, NJ; lot 101013) 20 ml pyrex test tubes. Brain, liver and kidneys were removed, weighed and stored individually in plastic specimen bags. Fecal samples (pellets) were removed from the large intestine, weighed and then stored in specimen bags. Sample collection required ~10 min/animal and samples were stored at -20 °C until analyzed.

Thallium Analysis

Thallium concentrations in samples were determined by electrothermal atomic absorption spectrometry (ET-AAS) (Perkin-Elmer Model 306 AAS equipped with a GF 2200 graphite furnace) using the Curry *et al.* (1969) procedure as modified by us. Tissue and fecal samples were wet ashed with 1 ml concentrated H_2SO_4 (Fisher trace metal grade, St. Louis, MO) and 3 ml concentrated HNO_3 (Fisher trace metal grade, St. Louis, MO) on a Corning hotplate at 70 °C. The sample digests were taken to a residual volume of ~1 ml and quantitatively transferred to acid-washed 50 ml polypropylene centrifuge tubes, then adjusted to pH 6.0 ± 0.1 with 6N NaOH (Fisher trace metal grade, St. Louis, MO). Freshly prepared 2% (w/v) sodium diethyldithiocarbamic acid (NDDC) (1 ml) was added and the mixture shaken by hand for 2 min to allow chelate complex

formation. Water-saturated methylisobutylketone (MIBK) (Fisher, St. Louis, MO) (1-5 ml) was added and the mixture shaken by hand for 3 min to extract the Tl-NDDC chelate complex into the organic phase. The samples were then centrifuged at 2500 rpm for 10 min to facilitate separation of the 2 immiscible phases. Aliquots of the upper organic phase (15 µl) were manually pipetted into the graphite furnace and peak heights recorded by a Perkin-Elmer Model 56 recorder. Blood samples were pretreated with an equal volume of 5% (w/v) trichloroacetic acid (TCA) (Fisher, St. Louis, MO) and shaken for 1 h to precipitate proteins. The mixture was centrifuged at 2500 rpm for 10 min and the supernatant transferred to a clean polypropylene centrifuge tube. The supernatant was then pH-adjusted, chelated with NDDC, extracted with MIBK, and analyzed as above. Standards were prepared in an identical manner using Tl-free rat tissues, feces and blood spiked with known amounts of the metal. All glass and plasticware were soaked for 24 h in a 20% (v/v) HCl bath, then soaked for 24 h in a 20% (v/v) HNO_3 bath, and thoroughly rinsed with DDW and air-dried prior to use. The safety precautions required for acid-digestion of biologic materials has been presented elsewhere (Mulkey and Oehme, 1993b).

The accuracy of the method was assessed by recovery studies. A series of 5 liver and 5 blood samples were spiked with 0.5, 1.0 or 10.0 µg Tl using a Tl nitrate standard (SPEX Industries, Edison, NJ) and then analyzed using the procedure

described above. Recoveries ranged from 96 to 101% for the liver samples and from 95 to 103% for the blood samples. The precision of the method, expressed as the coefficient of variation for liver and blood samples spiked with 1.0 µg Tl, was 12 and 14%, respectively.

Statistical Analysis

The experimental unit in this study was the individual rat. A statistical software package, SAS version 6.03, was used for data analysis (SAS Institute, Inc., 1988). Body weight, weight gain, organ weight/body weight (OW/BW) ratio, and Tl content data for each experimental group were examined for homogeneity of variance using Barlett's test and then compared by analysis of variance techniques (Gad and Weill, 1986) using SAS PROC GLM. Groups showing significant differences were further evaluated by multiple comparison testing using the Tukey-Kramer procedure (all data) or Duncan's multiple range test (weight gain and OW/BW ratio data only) (Ott, 1988). Survival rates for different groups were tested by the rxc chi-square test using SAS PROC FREQ and no significant differences were found. The 0.05 level of probability was used as the criterion of significance. Data are expressed as the mean ± standard error ($\bar{x}$ ± SE) unless otherwise indicated.

RESULTS

The 3 NT groups displayed overt signs of toxicity after being dosed with the equivalent of 20 mg Tl/kg BW po, as evidenced by a marked decrease in weight gain after exposure to the metal (Fig. 1). The T_{DMPS} group had only slightly greater weight gain than the NT_{DMPS} group. Both the T_{PB} and $T_{PB+DMPS}$ groups had much better weight gain after Tl intoxication than their respective untreated control groups. The post-exposure weight-gain rates of the T_{PB} and $T_{PB+DMPS}$ groups were only moderately reduced (97 and 83%, respectively) compared to their pre-exposure weight-gain rates. Clinical manifestations of acute Tl toxicity in NT group animals included diarrhea, slight tremor and gross hair loss upon handling (days 4-5), whereas no such effects were observed in T group animals, except for diarrhea and tremor in 2 NT_{DMPS} animals. NT_{PB} and NT_{DMPS} had 1 mortality each and $NT_{PB+DMPS}$ had 2 mortalities (n=7/gp) in contrast to the 3 T groups (n=10/gp) which had no deaths (Fig. 2).

Organ Weight/Body Weight Ratios

Organ weight/body weight (OW/BW) ratio data showed slight differences between T and NT groups with the exception of the T_{DMPS} group, which had significantly lower liver and kidney OW/BW ratios than its corresponding NT group ($p \leq 0.05$) (Fig. 3).

Thallium Content - Body Organs

The Tl content of selected body organs 5 d after Tl exposure is depicted in Fig. 4. We observed significant differences in the organ distribution pattern of Tl. The relative accumulation of Tl in body organs was kidney>> heart>liver≈brain, with kidney accumulation of Tl significantly greater ($p \leq 0.01$) than in other organs. The pattern of Tl deposition observed in this work and the Tl concentrations in blood and feces (discussed below) are in agreement with findings in previous studies (Thyresson, 1951; Sabbioni *et al.*, 1980; Manzo *et al.*, 1983; Rios *et al.*, 1989; Mulkey and Oehme, 1993c).

The T_{PB} group had significantly lower (30-50% of NT_{PB} group) Tl content in all organs compared to the NT_{PB} group ($p \leq 0.05$, brain, liver, heart; $p \leq 0.01$, kidney). The $T_{PB+DMPS}$ group had significantly reduced (30-47% of $NT_{PB+DMPS}$ group) Tl content than the $NT_{PB+DMPS}$ group ($p \leq 0.05$, brain, liver, heart; $p \leq 0.01$, kidney). In the T_{PB} and $T_{PB+DMPS}$ groups, more than a 3-fold reduction in brain (critical target organ) Tl levels occurred compared to the NT_{PB} and $NT_{PB+DMPS}$ groups; in contrast to the T_{DMPS} group, where only a minor decrease in Tl levels were noted.

Thallium Content - Blood and Feces

Fig. 5 shows the Tl content of whole blood and feces obtained at necropsy. The T_{PB} group had a significantly lower

(15% of NT_{PB} group) Tl concentration in blood compared to the NT_{PB} group ($p \leq 0.05$). The T_{DMPS} and $T_{PB+DMPS}$ groups had highly significant decreases (5 and 3% of NT_{DMPS} and $NT_{PB+DMPS}$ groups, respectively) in blood Tl concentrations compared to the NT_{DMPS} and $NT_{PB+DMPS}$ groups ($p \leq 0.01$). The T_{PB} and $T_{PB+DMPS}$ groups had 2.2-fold and 2.0-fold greater fecal Tl content compared to their respective control groups ($p \leq 0.05$ and $p \leq 0.01$, respectively). The difference between T_{DMPS} and NT_{DMPS} group fecal Tl content was negligible.

DISCUSSION

As evidenced by demonstrable clinical effects and as seen in Fig. 2, the Tl dosage used in this study was high enough to cause acute toxicity in NT group animals. At least 1 rat died in each NT group. As expected, the PB-treated animals were protected from the effects of Tl. None of the DMPS-treated animals died or showed signs of acute toxicity, despite accumulating substantial concentrations of Tl in several critical organs (Fig. 4). A possible explanation for this observation is that DMPS provided a protective effect against Tl poisoning by some undetermined mechanism (e.g., *in situ* inhibition of Tl's biologic activity) not measurable in terms of organ Tl content. Drawing such a conclusion, however, must be viewed with considerable skepticism. A more reasonable explanation for the lack of deaths in the T_{DMPS} group is that

the sample size of this group (n=10) was not large enough to detect the low incidence of lethal effect.

This study clearly shows that PB is an effective antidote in the treatment of thallotoxicosis. Prussian blue interrupts the enterohepatic circulation of Tl by adsorbing the metal ion within its crystal lattice (Rauws, 1974; Lehmann and Favari, 1984), but the extent to which this occurs *in vivo* is not well known. Treatment with PB probably resulted in the enteral dialysis of Tl^+; its reabsorption from the GI tract was blocked by adsorption to the complex cyanoferrate clathrate (Dvorák, 1969). Thus, fecal Tl^+ levels were significantly raised and tissue Tl levels were markedly reduced. The ion-exchange action of PB probably played the principal role in protecting the $T_{PB+DMPS}$ group animals from acute Tl toxicity.

Deductively, DMPS would be expected to decrease the body burden of Tl *in vivo*. The stability constant for the Tl-DMPS chelate complex is 1.43×10^{17} (Martell and Smith, 1982). Moreover, DMPS has been shown effective in enhancing the decorporation of other HSAB soft-acid metal ions, Ag^+ and Hg^{2+} (Gabard, 1976; Aaseth, 1983). The observation that DMPS enhances the biliary excretion of $^{203}Hg^{2+}$ (Cikrt and Tichy, 1980) provides a mechanistic basis for presuming that DMPS and PB would interact cooperatively to reduce Tl levels in acutely intoxicated rats. However, this was not the case. DMPS alone only marginally reduced organ Tl levels in the T group compared to its NT-group counterpart. Joint administration of

PB and DMPS likewise produced unremarkable results. The distribution of DMPS, a hydrophilic compound, is largely confined to the extracellular space (Catsch and Harmuth-Hoene, 1976; Gabard, 1978). DMPS's ineffectiveness in the treatment thallium toxicity may be due to its inability to access intracellular Tl deposits.

PB enhanced fecal elimination of Tl, but DMPS only marginally increased fecal Tl elimination. The reduced fecal Tl level observed in the $T_{PB+DMPS}$ group was likely due to enhanced urinary elimination of the metal, but this hypothesis was not proven in our study.

PB and DMPS significantly reduced the Tl concentration in whole blood. In blood, the PB+DMPS combination appeared to have had some cooperative effect in that Tl levels were reduced 5- and 1.6-fold compared to administration of the single antidotes.

Examination of OW/BW ratio data (Fig. 3) suggests that the T_{DMPS} group experienced hepatic and renal toxicity. This effect was not observed in the $T_{PB+DMPS}$ group. DMPS has been reported non-toxic at the dose (5 mg DMPS/kg BW ip) used in this study (Planas-Bohne *et al.*, 1980; Aposhian, 1983). The change in OW/BW ratios in these organs are likely due to increased Tl levels caused by mobilization of plasma Tl to kidney and liver as a Tl-DMPS complex, rather than to intrinsic toxicity of the chelator itself.

This study has shown that PB is an effective antidote for

acute Tl toxicity in rats, as evidenced by its ability to reduce Tl levels in 4 target organs -- kidney, liver, heart and brain. In contrast, the sole administration of DMPS failed to mobilize Tl in any organ. The combined use of PB+DMPS produced no significant changes in Tl levels in target organs compared to the use of PB alone. The chelator combination significantly reduced Tl concentrations in whole blood. Based on our findings and the reports of others (Lund, 1956; Heydlauf, 1969; Thompson, 1981; Rios and Monroy-Noyola, 1992), PB should continue to be considered the antidote of choice for treating acute thallium poisoning. The inability of DMPS to reduce Tl levels in target organs, when given singly or in combination with PB, suggests it is of little benefit in the treatment of thallotoxicosis.

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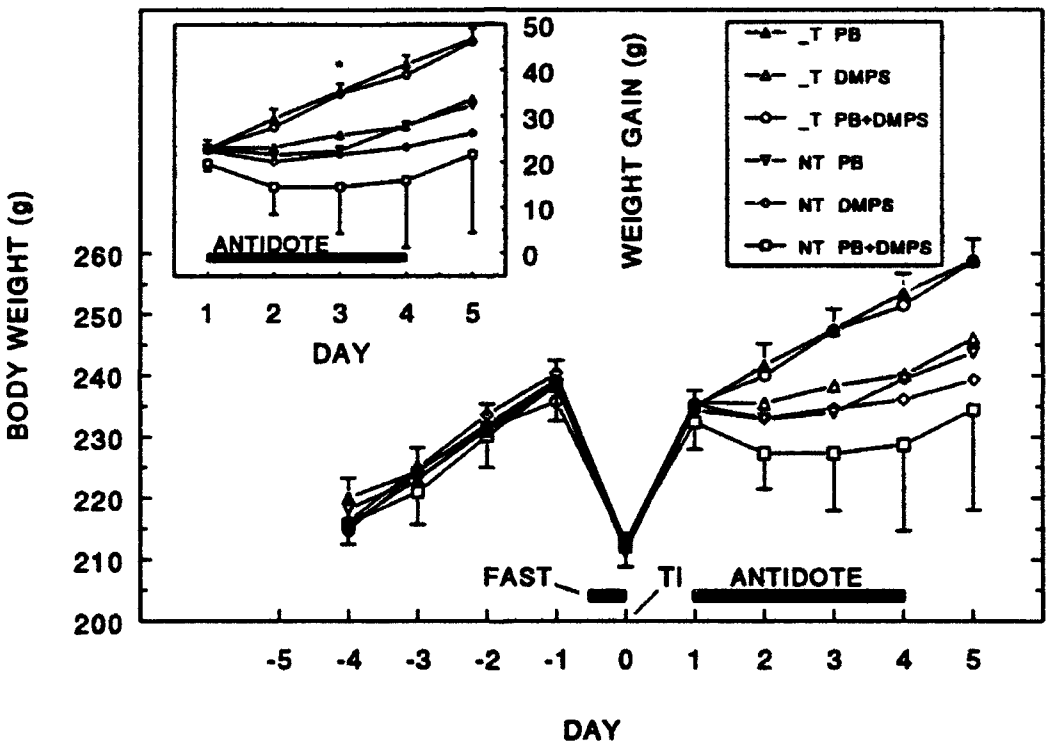
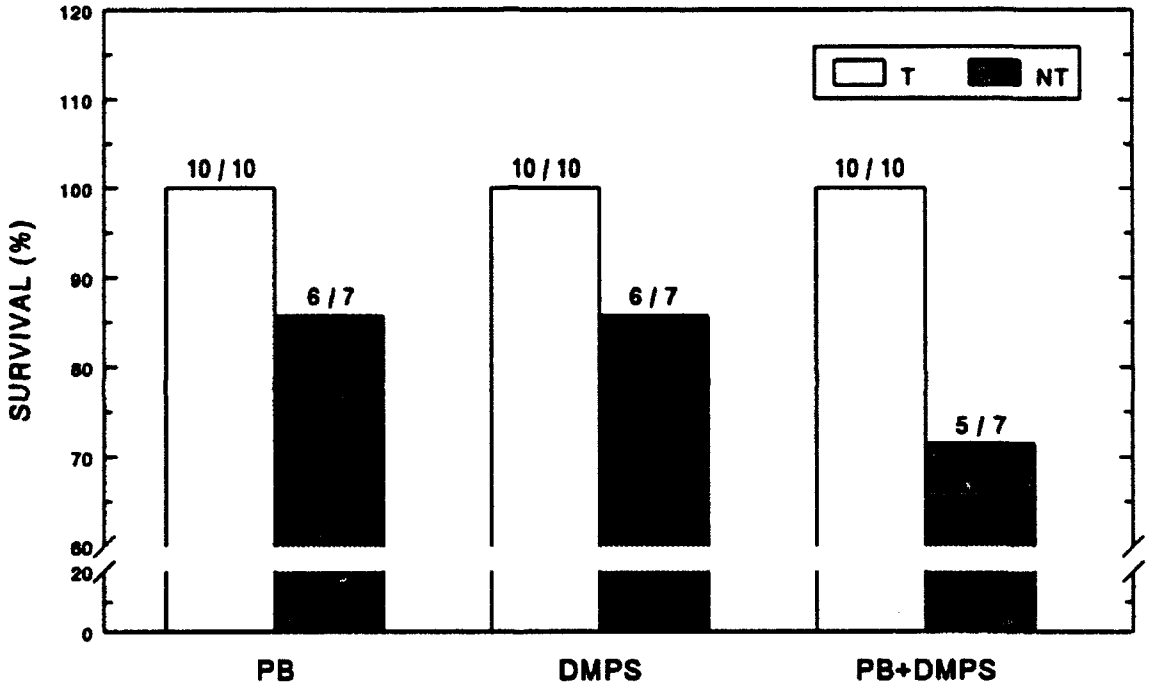
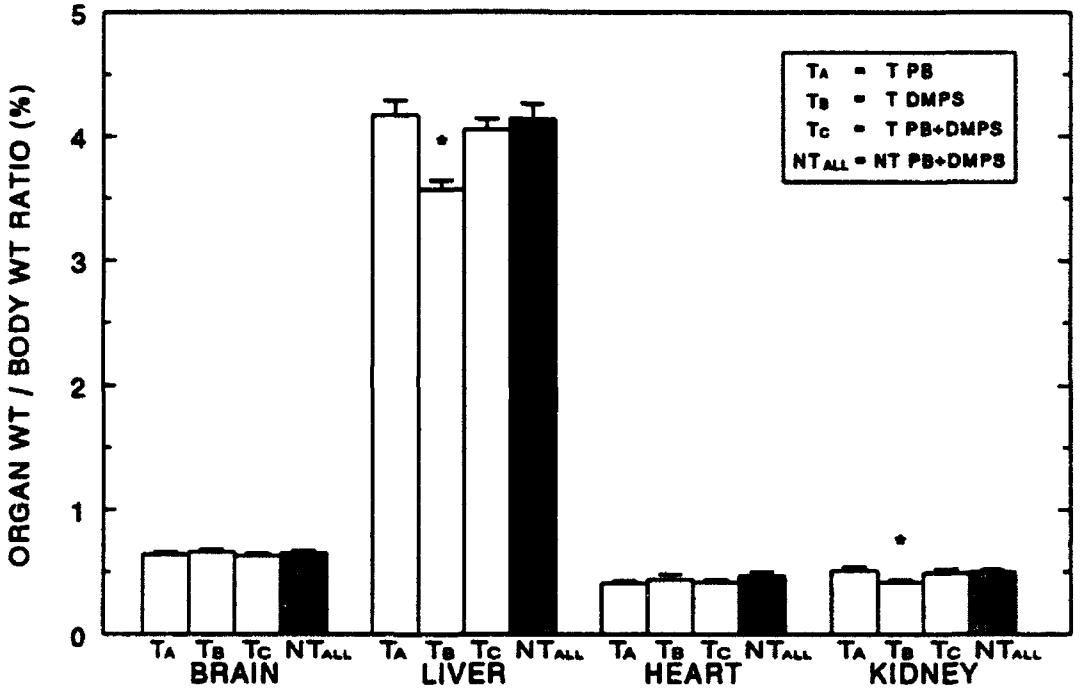
TABLE 1

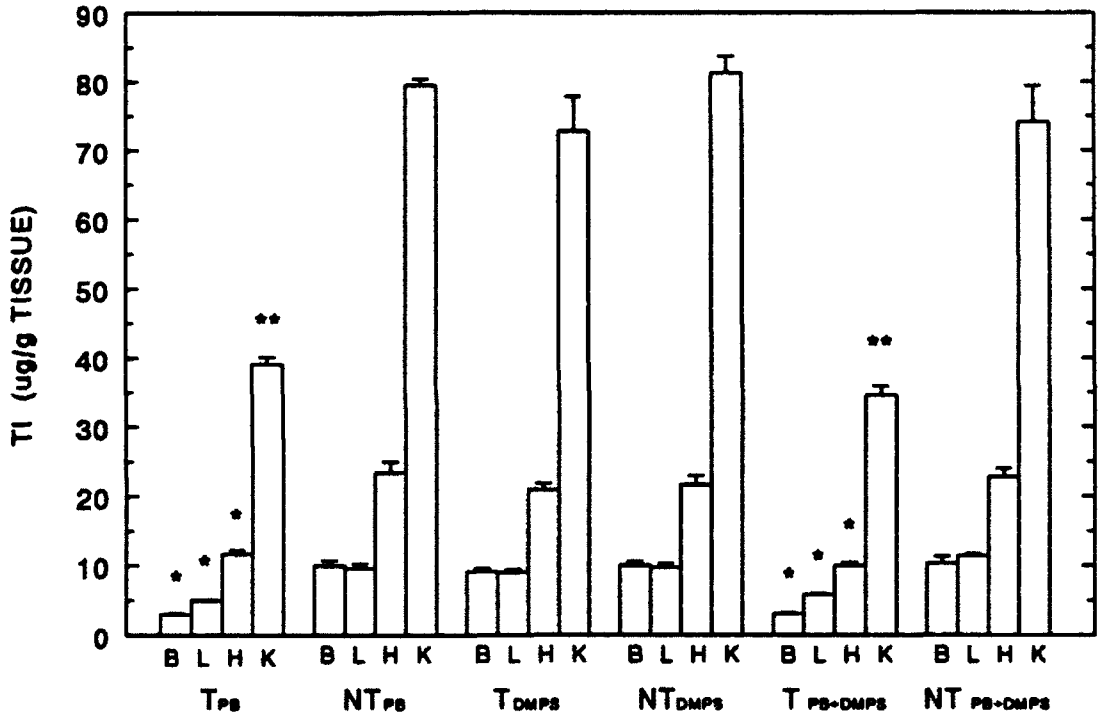
Antidote treatment schedule for the thallium antidote study. Treatment began 24 h after poisoning animals with the equivalent of 20 mg Tl/kg BW and was maintained for 4 d. Animals were sacrificed by ip phenobarbital 24 h after last antidotal treatment. (PB = prussian blue, potassium ferric hexacyanoferrate (II); DMPS = 2,3-dimercapto-1-propanesulfonic acid; T = treatment group; NT = non-treatment group)

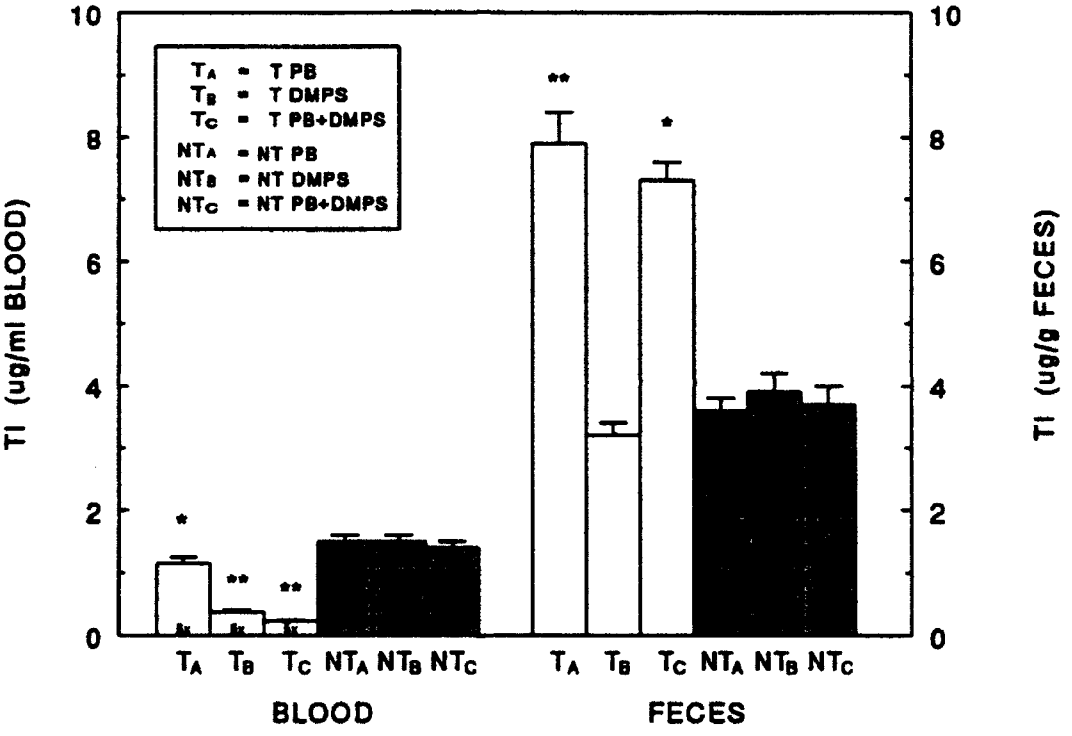
GROUPS	ANIMALS PER GROUP	DOSE	ROUTE	DOSES PER DAY	DAY
T_{PB}	10	50 mg PB/kg BW suspended in 1% Tween 80 (1 ml)	po	2	1-4
T_{DMPS}	10	5 mg DMPS/kg BW dissolved in DI H_2O (1 ml)	ip	6 4 2	1 2 3,4
$T_{PB+DMPS}$	10	50 mg PB/kg BW suspended in 1% Tween 80 (1 ml) 5 mg DMPS/kg BW dissolved in DI H_2O (1 ml)	po ip	2 6 4 2	1-4 1 2 3,4
NT_{PB}	7	1% Tween 80 (1 ml)	po	2	1-4
NT_{DMPS}	7	DI H_2O (1 ml)	ip	6 4 2	1 2 3,4
$NT_{PB+DMPS}$	7	1% Tween 80 (1 ml) DI H_2O (1 ml)	po ip	2 6 4 2	1-2 1 2 3,4


BODY WEIGHT (g)
260
250
240
230
220
210
200
-5
-4
-3
-2
-1
0
1
2
3
4
5
DAY
FAST
TI
ANTIDOTE
WEIGHT GAIN (g)
50
40
30
20
10
0
1
2
3
4
5
DAY
ANTIDOTE
_T PB
_T DMPS
_T PB+DMPS
NT PB
NT DMPS
NT PB+DMPS


SURVIVAL (%)
120
110
100
90
80
70
60
20
0
T
NT
10 / 10
6 / 7
10 / 10
6 / 7
10 / 10
5 / 7
PB
DMPS
PB+DMPS


ORGAN WT / BODY WT RATIO (%)
5
4
3
2
1
0
TA = T PB
TB = T DMPS
TC = T PB+DMPS
NTALL = NT PB+DMPS
TA TB TC NTALL
BRAIN
LIVER
HEART
KIDNEY


Tl (ug/g TISSUE)
90
80
70
60
50
40
30
20
10
0
B L H K
TPB
NTPB
TDMPS
NTDMPS
T PB+DMPS
NT PB+DMPS


TA = T PB
TB = T DMPS
TC = T PB+DMPS
NTA = NT PB
NTB = NT DMPS
NTC = NT PB+DMPS
TI (ug/ml BLOOD)
TI (ug/g FECES)
0
2
4
6
8
10
TA TB TC NTA NTB NTC
BLOOD
FECES

CAPTIONS

FIG. 1. The effect of acute thallium (Tl) toxicity (20 mg Tl/kg BW) and antidotal treatments on body weight (Main) and on daily weight gain (Insert). * Significantly different from corresponding control (NT) group ($p \leq 0.05$, Duncan's test after significant ANOVA). For clarity the SE's for only 1 treatment (T) and 1 NT group are shown; they are representative of the variation seen in the other T and NT groups. The large NT group SE's are due to the terminal weight loss of at least 1 rat/NT group. Data are expressed as the $x \pm$ SE (n=10/T gp; n=7/NT gp).

FIG. 2. The effect of antidotal treatment (T) or no treatment (NT) on the survival rates for different groups. PB = prussian blue; DMPS = Unithiol (2,3-dimercapto-1-propane-sulfonic acid). Numbers above bar are the number of survivors/total number of animals in each group.

FIG. 3. Organ weight/body weight ratios for different treatment (T) and non-treatment (NT) groups. For clarity, all NT groups are combined since there was little difference between the 3 NT groups. Significantly different from corresponding NT group ($p \leq 0.05$, Duncan's test after significant ANOVA). Results are expressed as $x \pm$ SE (n=10/T gp; n=7/NT gp). T = treatment gp; NT = non-treatment gp; A =

prussian blue (PB); B = Unithiol (DMPS); C = A+C (PB+DMPS).

FIG. 4. Thallium (Tl) content of body organs after dosing with 20 mg Tl/kg BW po and treatment with chelators (T gps) or respective suspending vehicle only (NT gps). Results are expressed as x ± SE (n=10/T gp; n=7/NT gp). T = treatment gp; NT = non-treatment gp; A = prussian blue (PB); B = Unithiol (DMPS); C = A+C (PB+DMPS); B = brain; L = liver; H = heart; K = kidney. Significant differences from untreated controls (Tukey-Kramer test after significant ANOVA): * ($p \leq 0.05$); ** ($p \leq 0.01$).

FIG. 5. Thallium (Tl) content in blood and feces after dosing with 20 mg Tl/kg BW po and treatment with chelators (T gps) or suspending vehicle only (NT gps). Results are expressed as x ± SE (n=10/T gp; n=7/NT gp). 5x = values shown are 5 times actual values. T = treatment gp; NT = non-treatment gp; A = prussian blue (PB); B = Unithiol (DMPS); C = A+C (PB+DMPS). Significant differences from untreated controls (Tukey-Kramer test after significant ANOVA): * ($p \leq 0.05$); ** ($p \leq 0.01$).

APPENDIX A

INDIVIDUAL ANIMAL DATA

WEIGHT TABLE

FILE ANT_WT_C

THALLIUM ANTIDOTE STUDY
CONSOLIDATED WEIGHT TABLE

DATE 2/6/93

WHOLE BODY WEIGHTS (g)

THALLIUM GIVEN | ANTIDOTE GIVEN DAY 1 – DAY 4 | ANIMALS SACRIFICED

TREATMENT GROUP	DAY -4	DAY -3	DAY -2	DAY -1	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	COMMENTS
PB											
CA 1		200	207	219	202	225	232	238	248	253	
CA 2		227	240	244	214	236	236	249	257	256	
CA 3	216	226	233	240	210	236	243	255	260	269	
CA 4	224	231	239	246	214	249	246	239	244	252	
CA 5	215	224	229	226	209	235	237	237	240	249	
CA 6	221	229	241	242	221	229	212	199	178	178	DIED DAY 4
CA 7	217	226	231	239	209	231	222	231	249	249	
MEAN	218.2	223.3	231.4	238.6	211.3	234.4	232.9	235.9	239.4	243.7	
STD DEV	4.3	10.5	11.7	8.3	5.9	7.6	12.9	19.6	28.0	29.6	
SEM	1.9	4.0	4.4	3.5	2.2	2.9	4.7	7.4	10.6	11.3	

RECEIVED VEHICLE ONLY: 1% TWEEN-80 po

TREATMENT GROUP	DAY -4	DAY -3	DAY -2	DAY -1	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	COMMENTS
DMPS											
CB 1		229	240	245	216	239	244	255	261	266	
CB 2		206	219	221	200	220	227	232	240	245	
CB 3	215	223	230	240	215	233	216	197	170	163	DIED DAY 5
CB 4	221	231	239	242	213	230	219	207	208	214	
CB 5	223	236	245	249	217	245	249	260	259	262	
CB 6	220	236	245	250	221	250	247	256	266	272	
CB 7	202	214	223	236	206	231	231	233	249	253	
MEAN	216.2	224.9	233.6	240.4	212.9	235.4	239.0	234.6	236.1	239.3	
STD DEV	8.5	10.7	10.3	9.9	6.9	10.1	13.5	25.1	35.6	38.7	
SEM	3.6	4.1	3.9	3.7	2.6	3.8	5.1	9.5	13.5	14.6	

RECEIVED VEHICLE ONLY: DI H2O ip

TREATMENT GROUP	DAY -4	DAY -3	DAY -2	DAY -1	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	COMMENTS
PB+DMPS											
CC 1		224	231	241	212	237	241	248	258	260	
CC 2		221	232	246	219	241	250	248	260	273	
CC 3		190	201	208	190	209	217	226	229	242	
CC 4	217	226	232	238	216	225	210	186	174	166	DIED DAY 5
CC 5	220	229	236	244	216	232	211	190	180	180	DIED DAY 4
CC 6	219	226	244	252	216	241	234	249	260	269	
CC 7	223	229	235	242	216	242	229	234	242	251	
MEAN	219.6	221.0	230.1	236.4	212.7	232.4	227.3	227.3	228.7	234.4	
STD DEV	2.5	14.0	13.6	15.0	10.3	12.0	15.4	25.0	37.1	43.4	
SEM	1.3	5.3	5.1	5.7	3.9	4.5	5.8	9.4	14.0	16.4	

RECEIVED VEHICLE ONLY: 1% TWEEN-80 po + DI H2O ip

FILE ANT_WT_C

THALLIUM ANTIDOTE STUDY
CONSOLIDATED WEIGHT TABLE

DATE 2/5/93

WHOLE BODY WEIGHTS (g)

THALLIUM GIVEN | ANTIDOTE GIVEN DAY 1 – DAY 4 | ANIMALS SACRIFICED

TREATMENT GROUP	DAY -4	DAY -3	DAY -2	DAY -1	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	COMMENTS
PB											
CA 1		200	207	219	202	225	232	236	248	253	
CA 2		227	240	244	214	236	236	246	257	258	
CA 3	216	226	238	240	210	236	243	255	260	269	
CA 4	224	231	239	248	214	240	246	239	244	252	
CA 5	213	224	229	236	208	235	237	237	240	249	
CA 6	221	229	241	242	221	229	212	193	178	178	DIED DAY 4
CA 7	217	226	231	239	208	231	222	231	249	249	
MEAN	218.2	223.3	231.4	238.6	211.3	234.4	232.6	233.9	238.4	243.7	
STD DEV	4.3	10.5	11.7	8.3	5.9	7.6	12.3	16.6	28.0	29.8	
SEM	1.9	4.0	4.4	3.5	2.2	2.9	4.7	7.4	10.6	11.3	

RECEIVED VEHICLE ONLY: 1% TWEEN-80 po

TREATMENT GROUP	DAY -4	DAY -3	DAY -2	DAY -1	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	COMMENTS
DMPS											
CB 1		228	240	245	216	239	244	255	261	268	
CB 2		208	219	221	200	230	227	232	240	245	
CB 3	215	223	230	240	215	236	216	197	170	163	DIED DAY 5
CB 4	221	231	233	242	213	230	218	207	208	214	
CB 5	223	236	245	248	217	245	248	260	259	262	
CB 6	220	236	245	250	221	250	247	258	268	272	
CB 7	202	214	223	236	208	231	231	236	249	253	
MEAN	216.2	224.9	233.6	240.4	212.9	235.4	233.0	234.6	238.1	239.3	
STD DEV	8.5	10.7	10.3	8.9	8.9	10.1	13.5	25.1	35.6	36.7	
SEM	3.8	4.1	3.9	3.7	2.8	3.8	5.1	9.5	13.5	14.6	

RECEIVED VEHICLE ONLY: DI H2O ip

TREATMENT GROUP	DAY -4	DAY -3	DAY -2	DAY -1	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	COMMENTS
PB+DMPS											
CC 1		224	231	241	212	237	241	248	256	260	
CC 2		221	232	246	219	241	250	246	260	273	
CC 3		190	201	208	180	200	217	226	229	242	
CC 4	217	226	232	236	210	226	210	196	174	168	DIED DAY 5
CC 5	220	229	236	244	218	232	211	190	180	180	DIED DAY 4
CC 6	219	228	244	252	216	241	234	248	260	269	
CC 7	223	229	236	242	218	242	228	234	242	251	
MEAN	219.8	221.0	230.1	238.4	212.7	232.4	227.3	227.3	228.7	234.4	
STD DEV	2.5	14.0	13.6	15.0	10.3	12.0	15.4	25.0	37.1	43.4	
SEM	1.3	5.3	5.1	5.7	3.9	4.5	5.8	9.4	14.0	16.4	

RECEIVED VEHICLE ONLY: 1% TWEEN-80 po + DI H2O ip

WEIGHT GAIN TABLE

FILE ANT_WT_C

THALLIUM ANTIDOTE STUDY
WEIGHT GAIN TABLE

DATE 2/5/88

CHANGE IN BODY WEIGHT FROM BASELINE MEASUREMENT AT DAY 0 (g)

THALLIUM GIVEN

ANTIDOTE GIVEN DAY 1 – DAY 4

ANIMALS SACRIFICED

T PS GROUP	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	COMMENTS
TA 1	0	16	16	30	41	43	
TA 2	0	20	28	39	39	43	
TA 3	0	22	28	30	35	50	
TA 4	0	22	32	38	40	47	
TA 5	0	20	34	40	47	56	
TA 6	0	24	30	36	41	56	
TA 7	0	22	30	38	42	56	
TA 8	0	21	35	37	40	39	
TA 9	0	21	33	44	55	35	
TA 10	0	20	31	30	42	43	
MEAN	0.0	20.6	28.5	35.4	41.4	46.6	
STD DEV	0.0	2.1	6.9	5.2	6.3	7.5	
SEM	0.0	0.7	2.2	1.7	2.0	2.4	

RECEIVED 50 mg PS / kg BW SUSPENDED IN 1% TWEEN–80 po

T DMPS GROUP	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	COMMENTS
TB 1	0	24	16	22	31	35	
TB 2	0	16	0	16	10	11	
TB 3	0	30	35	39	35	43	
TB 4	0	16	16	21	22	39	
TB 5	0	28	42	39	43	52	
TB 6	0	29	8	13	10	35	
TB 7	0	31	37	42	55	60	
TB 8	0	31	21	21	16	32	
TB 9	0	23	24	24	16	16	
TB 10	0	25	32	24	39	39	
MEAN	0.0	25.3	25.2	26.0	27.8	33.8	
STD DEV	0.0	4.7	13.6	10.1	14.8	13.0	
SEM	0.0	1.5	4.3	3.2	4.7	4.1	

RECEIVED 5 mg DMPS / kg BW DISSOLVED IN DI H20 ip

T PS+DMPS GROUP	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	COMMENTS
TC 1	0	30	18	35	39	35	
TC 2	0	10	4	27	30	39	
TC 3	0	23	28	35	46	47	
TC 4	0	24	35	41	43	55	
TC 5	0	28	40	50	54	77	
TC 6	0	22	30	47	55	62	
TC 7	0	26	35	40	39	44	
TC 8	0	27	33	24	21	31	
TC 9	0	23	28	28	37	30	
TC 10	0	28	34	32	44	39	
MEAN	0.0	22.9	27.5	34.9	38.1	46.3	
STD DEV	0.0	6.2	10.7	8.9	11.2	14.4	
SEM	0.0	1.8	3.4	2.8	3.6	4.6	

RECEIVED 50 mg PS / kg BW SUSPENDED IN 1% TWEEN–80 po + 5 mg DMPS / kg BW DISSOVED

FILE ANT_WT_C

THALLIUM ANTIDOTE STUDY
WEIGHT GAIN TABLE

DATE 2/6/89

CHANGE IN BODY WEIGHT FROM BASELINE MEASUREMENT AT DAY 0 (g)

THALLIUM GIVEN

ANTIDOTE GIVEN DAY 1 – DAY 4

ANIMALS SACRIFICED

NT PB GROUP	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	COMMENTS
CA 1	0	23	30	34	46	51	
CA 2	0	22	22	32	43	42	
CA 3	0	28	33	46	50	59	
CA 4	0	35	34	25	30	38	
CA 5	0	28	28	28	31	40	
CA 6	0	8	-9	-28	-43	-43	DIED DAY 4
CA 7	0	22	13	22	40	40	
MEAN	0.0	23.1	21.6	22.6	28.1	32.4	
STD DEV	0.0	8.1	15.3	23.5	32.2	34.1	
SEM	0.0	3.0	5.8	8.9	12.2	12.9	

RECEIVED VEHICLE ONLY: 1% TWEEN-80 po

NT DMPS GROUP	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	COMMENTS
CB 1	0	23	36	39	45	50	
CB 2	0	20	27	32	40	45	
CB 3	0	18	1	-18	-45	-52	DIED DAY 5
CB 4	0	17	5	-6	-7	1	
CB 5	0	28	31	43	42	45	
CB 6	0	29	28	37	47	61	
CB 7	0	23	23	25	41	46	
MEAN	0.0	22.6	20.1	21.7	23.3	26.4	
STD DEV	0.0	4.6	12.0	24.0	36.5	38.7	
SEM	0.0	1.8	4.5	9.1	13.4	14.6	

RECEIVED VEHICLE ONLY: DI H2O ip

NT PB+DMPS GROUP	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	COMMENTS
CC 1	0	25	29	35	44	48	
CC 2	0	22	31	29	41	54	
CC 3	0	19	27	36	39	52	
CC 4	0	9	-8	-20	-42	-50	DIED DAY 5
CC 5	0	14	-7	-28	-38	-38	DIED DAY 4
CC 6	0	25	16	33	44	53	
CC 7	0	34	10	16	24	33	
MEAN	0.0	19.7	14.6	14.6	16.0	21.7	
STD DEV	0.0	8.2	16.1	27.3	36.9	46.6	
SEM	0.0	2.9	6.1	10.3	14.7	17.2	

RECEIVED VEHICLE ONLY: 1% TWEEN-80 po + DI H2O ip

ORGAN WEIGHT TABLE

FILE ANT_ORGW

THALLIUM ANTIDOTE STUDY
CONSOLIDATED WEIGHT TABLE

DATE 2/5/93

ANIMAL ORGAN WEIGHTS (g)

T PB GROUP	LIVER	KIDNEY	HEART	BRAIN	COMMENTS
TA 1	10.26	1.37	0.92	1.71	
TA 2	8.47	1.18	1.13	1.60	
TA 3	10.85	1.38	1.21	1.82	
TA 4	11.02	1.70	0.89	1.72	
TA 5	10.85	1.14	1.26	1.76	
TA 6	12.59	1.61	1.36	1.82	
TA 7	11.65	1.14	1.04	1.74	
TA 8	9.89	1.14	1.02	1.62	
TA 9	10.51	1.55	0.92	1.64	
TA 10	12.06	1.19	0.90	1.56	
MEAN	10.80	1.34	1.07	1.66	
STD DEV	1.16	0.22	0.17	0.07	
SEM	0.37	0.07	0.05	0.02	

T DMPS GROUP	LIVER	KIDNEY	HEART	BRAIN	COMMENTS
TB 1	8.83	1.27	1.17	1.64	
TB 2	8.96	1.15	1.12	1.53	
TB 3	8.96	0.80	1.19	1.42	
TB 4	8.76	0.93	0.94	1.65	
TB 5	8.52	1.22	0.86	1.67	
TB 6	8.88	1.00	0.90	1.57	
TB 7	8.41	1.31	1.12	1.60	
TB 8	8.47	1.00	0.92	1.71	
TB 9	8.38	0.96	1.36	1.61	
TB 10	8.95	0.96	1.06	1.80	
MEAN	8.71	1.04	1.07	1.62	
STD DEV	0.24	0.21	0.16	0.10	
SEM	0.08	0.07	0.05	0.03	

T PB+DMPS GROUP	LIVER	KIDNEY	HEART	BRAIN	COMMENTS
TC 1	10.25	1.27	1.12	1.55	
TC 2	9.67	1.40	0.92	1.64	
TC 3	10.25	1.20	1.13	1.86	ONLY 1 KIDNEY
TC 4	10.28	1.18	1.22	1.67	
TC 5	11.61	1.32	1.37	1.52	
TC 6	10.29	1.40	1.04	1.75	
TC 7	10.12	1.41	1.26	1.60	
TC 8	10.38	1.25	0.93	1.59	
TC 9	10.63	1.29	0.99	1.39	
TC10	10.84	1.42	0.91	1.66	
MEAN	10.43	1.31	1.09	1.63	
STD DEV	0.51	0.09	0.16	0.13	
SEM	0.16	0.03	0.05	0.04	

FILE ANT_ORGW

THALLIUM ANTIDOTE STUDY
CONSOLIDATED WEIGHT TABLE

DATE 2/5/93

ANIMAL ORGAN WEIGHTS (g)

NT PB GROUP	LIVER	KIDNEY	HEART	BRAIN	COMMENTS
CA 1	10.94	1.16	1.25	1.55	
CA 2	9.61	1.30	0.99	1.51	
CA 3	9.61	1.11	0.97	1.68	
CA 4	10.39	1.11	0.94	1.52	
CA 5	10.31	1.01	1.15	1.52	
CA 6	9.60	1.16	0.84	1.39	DIED DAY 4
CA 7	8.29	1.16	1.36	1.57	
MEAN	9.82	1.15	1.07	1.53	
STD DEV	0.85	0.09	0.19	0.09	
SEM	0.32	0.03	0.07	0.03	

NT DMPS GROUP	LIVER	KIDNEY	HEART	BRAIN	COMMENTS
CB 1	9.71	1.20	1.31	1.51	
CB 2	9.61	1.01	1.34	1.50	
CB 3	6.99	0.95	0.94	1.42	DIED DAY 5
CB 4	11.41	1.31	0.87	1.59	
CB 5	9.27	1.32	1.29	1.61	
CB 6	11.88	1.30	1.35	1.52	
CB 7	10.75	1.29	1.09	1.55	
MEAN	9.95	1.20	1.17	1.53	
STD DEV	1.63	0.15	0.20	0.06	
SEM	0.62	0.06	0.08	0.02	

NT PB+DMPS GROUP	LIVER	KIDNEY	HEART	BRAIN	COMMENTS
CC 1	11.04	1.24	1.39	1.50	
CC 2	12.56	1.24	1.22	1.63	
CC 3	10.01	1.00	1.20	1.52	
CC 4	6.19	1.03	0.89	1.44	DIED DAY 5
CC 5	8.98	1.21	0.84	1.46	DIED DAY 4
CC 6	9.83	1.19	1.07	1.61	
CC 7	9.13	1.13	1.35	1.54	
MEAN	9.68	1.15	1.14	1.53	
STD DEV	1.97	0.10	0.21	0.07	
SEM	0.74	0.04	0.08	0.03	

FILE ANT_ORGW

THALLIUM ANTIDOTE STUDY
CONSOLIDATED WEIGHT TABLE

DATE 2/5/93

ANIMAL ORGAN WEIGHTS (g)

GROUP	LIVER	KIDNEY	HEART	BRAIN	COMMENTS
CA 1	10.94	1.16	1.25	1.55	
CA 2	9.61	1.30	0.99	1.51	
CA 3	9.61	1.11	0.97	1.66	
CA 4	10.39	1.11	0.94	1.52	
CA 5	10.31	1.01	1.15	1.52	
CA 6	9.60	1.18	0.84	1.39	DIED DAY 4
CA 7	8.29	1.16	1.36	1.57	
CB 1	9.71	1.20	1.31	1.51	
CB 2	9.61	1.01	1.34	1.50	
CB 3	8.99	0.95	0.94	1.42	DIED DAY 5
CB 4	11.41	1.31	0.87	1.59	
CB 5	9.27	1.32	1.29	1.61	
CB 6	11.88	1.30	1.35	1.52	
CB 7	10.75	1.29	1.09	1.55	
CC 1	11.04	1.24	1.39	1.50	
CC 2	12.56	1.24	1.22	1.63	
CC 3	10.01	1.00	1.20	1.52	
CC 4	8.19	1.03	0.89	1.44	DIED DAY 5
CC 5	8.98	1.21	0.84	1.46	DIED DAY 4
CC 6	9.83	1.19	1.07	1.61	
CC 7	9.13	1.13	1.36	1.54	
MEAN	9.81	1.16	1.13	1.53	
STD DEV	1.48	0.11	0.20	0.07	
SEM	0.32	0.02	0.04	0.02	

ORGAN WEIGHT/BODY WEIGHT RATIO TABLE

FILE ANT_ORG THALLIUM ANTIDOTE STUDY DATE 2/5/93

ORGAN WEIGHT / BODY WEIGHT RATIO TABLE (%)

GROUP	ORGAN WEIGHT / BODY WEIGHT RATIO (%)				COMMENTS
	LIVER	KIDNEY	HEART	BRAIN	
TA 1	4.13	0.55	0.37	0.69	
TA 2	3.47	0.48	0.46	0.66	
TA 3	3.99	0.51	0.44	0.60	
TA 4	4.27	0.66	0.34	0.67	
TA 5	3.96	0.42	0.47	0.65	
TA 6	4.56	0.58	0.49	0.59	
TA 7	4.41	0.43	0.39	0.66	
TA 8	3.85	0.44	0.40	0.63	
TA 9	4.17	0.62	0.37	0.65	
TA 10	4.66	0.48	0.36	0.63	
MEAN	4.17	0.52	0.41	0.64	
STD DEV	0.39	0.08	0.05	0.03	
SEM	0.12	0.03	0.02	0.01	

GROUP	ORGAN WEIGHT / BODY WEIGHT RATIO (%)				COMMENTS
	LIVER	KIDNEY	HEART	BRAIN	
TB 1	3.77	0.54	0.50	0.70	
TB 2	4.05	0.52	0.50	0.69	
TB 3	3.39	0.23	0.45	0.54	
TB 4	3.67	0.39	0.39	0.69	
TB 5	3.12	0.45	0.32	0.61	
TB 6	3.67	0.41	0.37	0.65	
TB 7	3.19	0.49	0.42	0.61	
TB 8	3.51	0.41	0.38	0.71	
TB 9	3.60	0.42	0.56	0.69	
TB 10	3.59	0.36	0.43	0.72	
MEAN	3.56	0.42	0.44	0.66	
STD DEV	0.27	0.09	0.06	0.06	
SEM	0.09	0.03	0.02	0.02	

GROUP	ORGAN WEIGHT / BODY WEIGHT RATIO (%)				COMMENTS
	LIVER	KIDNEY	HEART	BRAIN	
TC 1	3.97	0.49	0.43	0.60	
TC 2	3.78	0.55	0.36	0.64	
TC 3	3.73	0.22	0.41	0.68	
TC 4	3.94	0.45	0.47	0.64	
TC 5	3.81	0.43	0.45	0.50	
TC 6	3.78	0.51	0.38	0.64	
TC 7	4.27	0.59	0.53	0.68	
TC 8	4.40	0.53	0.39	0.67	
TC 9	4.36	0.53	0.41	0.57	
TC 10	4.46	0.58	0.37	0.68	
MEAN	4.05	0.49	0.42	0.63	
STD DEV	0.29	0.11	0.05	0.06	
SEM	0.09	0.03	0.02	0.02	

FILE ANT_ORG THALLIUM ANTIDOTE STUDY DATE 2/5/93

ORGAN WEIGHT / BODY WEIGHT RATIO TABLE (%)

GROUP	ORGAN WEIGHT / BODY WEIGHT RATIO (%)				COMMENTS
	LIVER	KIDNEY	HEART	BRAIN	
CA 1	4.32	0.46	0.49	0.61	
CA 2	3.75	0.51	0.39	0.59	
CA 3	3.57	0.41	0.36	0.62	
CA 4	4.12	0.44	0.37	0.60	
CA 5	4.14	0.41	0.46	0.61	
CA 6	5.39	0.66	0.47	0.78	DIED DAY 4
CA 7	3.33	0.47	0.55	0.63	
MEAN	4.09	0.48	0.44	0.64	
STD DEV	0.67	0.09	0.07	0.07	
SEM	0.25	0.03	0.03	0.02	

GROUP	ORGAN WEIGHT / BODY WEIGHT RATIO (%)				COMMENTS
	LIVER	KIDNEY	HEART	BRAIN	
CB 1	3.65	0.45	0.49	0.57	
CB 2	3.92	0.41	0.55	0.61	
CB 3	4.29	0.56	0.56	0.67	DIED DAY 5
CB 4	5.33	0.61	0.41	0.74	
CB 5	3.54	0.50	0.49	0.61	
CB 6	4.37	0.46	0.50	0.56	
CB 7	4.25	0.51	0.43	0.61	
MEAN	4.19	0.51	0.49	0.65	
STD DEV	0.60	0.07	0.06	0.11	
SEM	0.23	0.03	0.02	0.04	

GROUP	ORGAN WEIGHT / BODY WEIGHT RATIO (%)				COMMENTS
	LIVER	KIDNEY	HEART	BRAIN	
CC 1	4.25	0.48	0.53	0.56	
CC 2	4.60	0.45	0.45	0.60	
CC 3	4.14	0.41	0.50	0.63	
CC 4	3.73	0.62	0.54	0.67	DIED DAY 5
CC 5	4.99	0.67	0.47	0.81	DIED DAY 4
CC 6	3.65	0.44	0.40	0.60	
CC 7	3.84	0.45	0.54	0.61	
MEAN	4.14	0.50	0.49	0.67	
STD DEV	0.52	0.10	0.06	0.12	
SEM	0.20	0.04	0.02	0.04	

FILE ANT_ORG THALLIUM ANTIDOTE STUDY DATE 2/5/93

ORGAN WEIGHT / BODY WEIGHT RATIO TABLE (%)

GROUP	ORGAN WEIGHT / BODY WEIGHT RATIO (%)				COMMENTS
	LIVER	KIDNEY	HEART	BRAIN	
CA 1	4.32	0.46	0.49	0.61	
CA 2	3.75	0.51	0.39	0.59	
CA 3	3.57	0.41	0.36	0.62	
CA 4	4.12	0.44	0.37	0.60	
CA 5	4.14	0.41	0.46	0.61	
CA 6	5.39	0.66	0.47	0.78	DIED DAY 4
CA 7	3.33	0.47	0.55	0.63	
CB 1	3.65	0.45	0.49	0.57	
CB 2	3.92	0.41	0.56	0.61	
CB 3	4.29	0.58	0.58	0.87	DIED DAY 5
CB 4	5.33	0.61	0.41	0.74	
CB 5	3.54	0.50	0.49	0.61	
CB 6	4.37	0.48	0.50	0.56	
CB 7	4.25	0.51	0.43	0.61	
CC 1	4.25	0.48	0.53	0.56	
CC 2	4.60	0.45	0.45	0.60	
CC 3	4.14	0.41	0.50	0.63	
CC 4	3.73	0.62	0.54	0.87	DIED DAY 5
CC 5	4.99	0.67	0.47	0.81	DIED DAY 4
CC 6	3.65	0.44	0.40	- 0.60	
CC 7	3.64	0.45	0.54	0.61	
MEAN	4.14	0.50	0.47	0.65	
STD DEV	0.57	0.08	0.06	0.10	
SEM	0.12	0.02	0.01	0.02	

THALLIUM CONTENT OF

ORGANS, BLOOD AND FECES

THALLIUM CONTENT (ppm) OF
RAT ORGANS, BLOOD & FECES

PB TREATMENT GROUP	THALLIUM CONTENT (ppm) KIDNEY	LIVER	HEART	BRAIN	BLOOD	FECES	COMMENTS
TA 1	37.4	5.7	14.8	3.1	0.27	9.7	
TA 2	44.1	5.3	13.7	2.7	0.34	6.8	
TA 3	38.7	5.5	9.6	4.5	0.16	6.5	
TA 4	40.6	4.6	9.4	2.6	0.17	5.7	
TA 5	34.4	4.3	9.2	3.4	0.33	7.0	
TA 6	40.6	5.0	12.3	3.3	0.27	7.3	
TA 7	41.6	4.9	12.3	2.7	0.25	10.9	
TA 8	39.9	5.2	13.0	2.2	0.26	7.0	
TA 9	34.7	4.6	11.9	2.9	0.21	7.6	
TA 10	36.7	5.1	11.3	2.9	0.17	6.6	
MEAN	39.2	5.0	11.7	3.0	0.23	7.9	
STD DEV	3.0	0.4	1.9	0.6	0.06	1.5	
SEM	1.0	0.1	0.6	0.2	0.02	0.5	

RECEIVED 50 mg PB / kg BW SUSPENDED IN 1% TWEEN-80 po

DMPS TREATMENT GROUP	THALLIUM CONTENT (ppm) KIDNEY	LIVER	HEART	BRAIN	BLOOD	FECES	COMMENTS
TB 1	66.1	10.2	21.4	9.5	0.071	3.6	
TB 2	52.2	9.5	22.2	12.1	0.073	3.6	
TB 3	50.8	8.4	16.1	6.8	0.076	3.1	
TB 4	84.1	7.6	18.6	9.6	0.112	3.9	
TB 5	86.0	9.0	19.8	10.7	0.102	2.8	
TB 6	90.5	8.2	24.7	7.4	0.080	4.2	
TB 7	74.0	8.2	25.4	9.5	0.058	3.6	
TB 8	76.8	11.4	19.7	6.6	0.066	2.6	
TB 9	70.3	7.6	22.1	8.4	0.068	2.2	
TB 10	77.1	9.4	20.7	6.4	0.070	2.2	
MEAN	72.6	9.0	21.0	9.2	0.075	3.2	
STD DEV	15.7	1.2	2.6	1.6	0.016	0.7	
SEM	5.0	0.4	0.9	0.5	0.006	0.2	

RECEIVED 5 mg DMPS / kg BW DISSOLVED IN DI H2O ip

DMPS + PB TREATMENT GROUP	THALLIUM CONTENT (ppm) KIDNEY	LIVER	HEART	BRAIN	BLOOD	FECES	COMMENTS
TC 1	36.6	5.7	10.1	2.6	0.069	7.3	
TC 2	37.3	5.3	11.3	2.6	0.054	7.2	
TC 3	37.6	5.4	13.5	2.4	0.065	5.8	
TC 4	29.3	5.5	10.7	3.0	0.057	7.3	
TC 5	29.3	5.2	8.5	4.2	0.058	9.1	
TC 6	39.3	7.5	10.2	3.0	0.040	6.7	
TC 7	39.4	5.8	7.6	3.5	0.041	7.7	
TC 8	34.5	6.0	8.6	2.4	0.037	6.4	
TC 9	27.2	6.6	8.6	3.1	0.032	6.7	
TC 10	35.6	6.2	8.3	2.4	0.056	6.9	
MEAN	34.6	5.9	10.0	3.1	0.047	7.3	
STD DEV	4.4	0.7	1.6	0.7	0.012	1.0	
SEM	1.4	0.2	0.5	0.2	0.004	0.3	

RECEIVED 50 mg PB / kg BW SUSPENDED IN 1% TWEEN-80 po + 5 mg DMPS / kg BW DISSOLVED IN DI H2O ip

THALLIUM CONTENT (ppm) OF
RAT ORGANS, BLOOD & FECES

PB CONTROL GROUP	THALLIUM CONTENT (ppm) KIDNEY	LIVER	HEART	BRAIN	BLOOD	FECES	COMMENTS
CA 1	79.5	9.4	19.5	10.8	1.3	3.7	
CA 2	76.8	8.1	24.8	10.2	1.9	2.7	
CA 3	80.8	9.0	24.8	11.9	1.3	3.8	
CA 4	75.3	8.2	19.9	7.2	1.2	4.0	
CA 5	76.9	10.2	19.9	7.2	1.1	3.6	
CA 6	63.6	12.6	30.0	12.9	2.1	2.9	DIED DAY 4
CA 7	79.5	10.2	25.6	9.8	1.4	4.4	
MEAN	79.5	9.7	23.5	10.0	1.5	3.6	
STD DEV	2.5	1.6	3.9	2.2	0.4	0.6	
SEM	0.9	0.6	1.5	0.8	0.1	0.2	

RECEIVED VEHICLE ONLY: 1% TWEEN-80 po

DMPS CONTROL GROUP	THALLIUM CONTENT (ppm) KIDNEY	LIVER	HEART	BRAIN	BLOOD	FECES	COMMENTS
CB 1	87.0	10.4	22.4	8.5	1.0	3.4	
CB 2	72.0	8.7	19.4	8.4	1.7	4.3	
CB 3	90.5	12.3	28.6	13.4	1.8	3.2	DIED DAY 5
CB 4	74.5	9.1	19.3	10.1	0.8	4.5	
CB 5	83.1	8.6	18.5	7.9	1.4	2.9	
CB 6	81.8	9.7	22.3	10.4	1.9	4.3	
CB 7	79.8	9.8	20.2	9.0	1.9	4.7	
MEAN	81.2	9.8	21.7	10.0	1.5	3.9	
STD DEV	6.5	1.3	3.8	1.7	0.4	0.7	
SEM	2.5	0.5	1.3	0.6	0.1	0.3	

RECEIVED VEHICLE ONLY: DI H2O ip

PB + DMPS CONTROL GROUP	THALLIUM CONTENT (ppm) KIDNEY	LIVER	HEART	BRAIN	BLOOD	FECES	COMMENTS
CC 1	55.3	10.9	22.5	10.3	1.7	3.4	
CC 2	61.7	11.4	21.5	8.8	1.0	2.9	
CC 3	64.0	10.5	18.3	9.2	1.1	3.2	
CC 4	90.5	12.4	29.0	13.8	1.7	5.1	
CC 5	92.3	12.3	23.3	14.2	1.8	4.5	DIED DAY 5
CC 6	66.8	10.1	22.7	7.8	1.5	3.1	DIED DAY 4
CC 7	66.9	11.9	21.8	8.1	1.4	3.4	
MEAN	74.2	11.4	22.8	10.3	1.4	3.7	
STD DEV	14.1	0.9	3.2	2.6	0.3	0.8	
SEM	5.3	0.3	1.2	1.0	0.1	0.3	

RECEIVED VEHICLE ONLY: 1% TWEEN-80 po + DI H2O ip

CLINICAL OBSERVATIONS

CLINICAL OBSERVATIONS TABLE

The clinical effects of thallium poisoning in rats are diarrhea, tremor, and alopecia, whereas scruffy coat is non-specific sign of illness. Animals having these signs are indicated below.

GROUP	DIARRHEA	TREMOR	SCRUFFY COAT	ALOPECIA
TA	N/A	N/A	N/A	N/A
TB	TB2 TB4	TB2 TB4	N/A	N/A
TC	N/A	N/A	N/A	N/A
CA	CA5 CA6	CA1 CA6	CA1 CA6	CA6
CB	CB5 CB3	CB6 CB3	CB6 CB3	CB3
CC	CC4 CC5	CC4 CC5	CC4 CC5	CC4 CC5

TA = Prussian blue (PB) treatment (T) group; TB = Unithiol (DMPS) T group; TC = PB+DMPS T group; CA = PB non-treatment (NT) group; CB = DMPS NT group; CC = PB+DMPS NT group; N/A = not applicable

Observations from gross examination of animals that died before the end of the study:

CA6 none; had minimal amount of fecal matter in bowel.

CB3 colon distended with bloody serous liquid; no ulceration observed.

CC4 enlarged, distended colon containing 2.7 g feces; dimensions of enlarged colon 3.5 x 3.1 x 1.9 cm; lower left and right lobes had patchy dark-red areas.

CC5 small amount of liquid feces (no pellets).

APPENDIX B

THALLIUM DETERMINATION WORKSHEETS

KIDNEY

FILE A_A_K1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/10/93

SAMPLE: KIDNEY

GROUPS: PB (TX & NO TX)

RUN 1 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.1					5.1
0.10	17.1					17.1
0.30	60.2					60.2
0.50	90.2					90.2
0.70	110.4					110.4
1.00	157.0					157.0

RUN 2 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	4.6					4.6
0.1	15.9					15.9
0.3	58.3					58.3
0.5	83.6					83.6
0.7	116.2					116.2
1.00	162.0					162.0

RUN 3 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	3.5					3.5
0.1	14.8					14.8
0.3	58.4					58.4
0.5	77.2					77.2
0.7	115.2					115.2
1.00	162.4					162.4

FILE A_A_K1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/10/93

SAMPLE: KIDNEY

GROUPS: PB (TX & NO TX)

Tl STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	2.9	0.9	−0.4
0.05	5.1	4.6	3.5	10.9	9.1	7.8
0.10	17.1	15.9	14.8	18.8	17.3	16.0
0.30	60.2	58.3	58.4	50.4	50.1	48.8
0.50	90.2	83.6	77.2	82.1	82.9	81.5
0.70	110.4	116.2	115.2	113.7	115.7	114.3
1.00	157.0	162.0	162.4	161.2	164.9	163.4

Regression Output:	RUN 1
Constant	2.9407234
Std Err of Y Est	6.8553053
R Squared	0.9889467
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	158.26978
Std Err of Coef.	7.4829335

Regression Output:	RUN 3
Constant	−0.361021
Std Err of Y Est	5.1698727
R Squared	0.9940892
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	163.78382
Std Err of Coef.	5.6431934

Regression Output:	RUN 2
Constant	0.8532765
Std Err of Y Est	4.4586333
R Squared	0.9956165
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	164.01021
Std Err of Coef.	4.8668374

Regression Output:	3 STD RUNS COMBINED
Constant	1.1443262
Std Err of Y Est	5.0946372
R Squared	0.9925941
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	162.02127
Std Err of Coef.	3.2106851

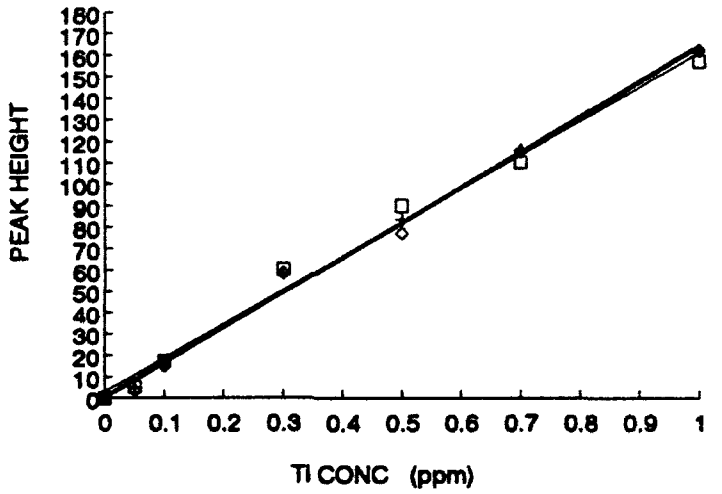
FILE A_A_K1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/10/93

SAMPLE: KIDNEY

GROUPS: PB (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE TI CONC (ppm)
TA 1	76.5	78.4			77.5	0.47
TA 2	85.0	84.6			84.8	0.52
TA 3	89.6	88.8			89.2	0.54
TA 4	85.0	80.0			82.5	0.50
TA 5	77.2	72.0			74.6	0.45
TA 6	80.4	85.4			82.9	0.50
TA 7	77.0	74.2			75.6	0.46
TA 8	83.6	83.4			83.5	0.51
TA 9	70.4	76.0			73.2	0.44
TA 10	83.0	80.3			81.7	0.50
CA 1	82.0	79.6			80.8	0.49
CA 2	81.0	73.2			77.1	0.47
CA 3	81.8	79.2			80.5	0.49
CA 4	67.0	62.4			64.7	0.39
CA 5	73.0	76.8			74.9	0.46
CA 6	70.8	73.8			72.3	0.44
CA 7	81.8	79.4			80.6	0.49

TI CONC = (y - b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/9/93

FILE: A_A_K2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: KIDNEY
PB

DATE ANALYZED: 2/10/93

PATH: c:\data\lotus2.3
a:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	Tl CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A – B			D x E		F x G / C	
TA 1	61.6620	61.4102	0.2518	5.0	4	20	0.47	37.41	
TA 2	60.1808	59.9468	0.2340	5.0	4	20	0.52	44.13	
TA 3	58.5971	58.3232	0.2739	5.0	4	20	0.54	39.68	
TA 4	60.7675	60.5203	0.2472	5.0	4	20	0.50	40.63	
TA 5	61.9423	61.6787	0.2636	5.0	4	20	0.45	34.40	
TA 6	49.6325	49.3839	0.2486	5.0	4	20	0.50	40.60	
TA 7	48.8225	48.6016	0.2209	5.0	4	20	0.46	41.81	
TA 8	49.1424	48.8875	0.2549	5.0	4	20	0.51	39.88	
TA 9	60.4747	60.2186	0.2561	5.0	4	20	0.44	34.73	
TA 10	62.2599	62.0032	0.2567	5.0	4	20	0.50	38.71	
CA 1	49.3483	49.1010	0.2473	5.0	8	40	0.49	79.52	
CA 2	56.8709	56.6329	0.2380	5.0	8	40	0.47	78.79	
CA 3	50.3318	50.0883	0.2435	5.0	8	40	0.49	80.78	
CA 4	62.2650	62.0565	0.2085	5.0	8	40	0.39	75.26	
CA 5	62.3711	62.1404	0.2307	5.0	8	40	0.46	78.93	
CA 6	62.8982	62.6882	0.2101	5.0	8	40	0.44	83.61	DIED DAY 4
CA 7	61.7957	61.5490	0.2467	5.0	8	40	0.49	79.51	
MEAN			0.2431						

FILE A_B_K1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/12/93

SAMPLE: KIDNEY

GROUPS: DMPS (TX & NO TX)

RUN 1 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	4.1					4.1
0.10	9.9					9.9
0.30	42.2					42.2
0.50	75.6					75.6
0.70	88.4					88.4
1.00	134.2					134.2

RUN 2 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	4.0					4.0
0.1	9.7					9.7
0.3	41.3					41.3
0.5	76.0					76.0
0.7	92.2					92.2
1.00	136.6					136.6

RUN 3 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	3.8					3.8
0.1	9.5					9.5
0.3	40.8					40.8
0.5	71.4					71.4
0.7	89.2					89.2
1.00	136.2					136.2

FILE A_B_K1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/12/93

SAMPLE: KIDNEY

GROUPS: DMPS (TX & NO TX)

Tl STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	−0.8	−1.1	−1.7
0.05	4.1	4.0	3.8	6.2	5.8	5.2
0.10	9.9	9.7	9.5	12.9	12.7	12.0
0.30	42.2	41.3	40.8	40.0	40.5	39.4
0.50	75.6	76.0	71.4	67.1	68.3	66.7
0.70	88.4	92.2	89.2	94.1	96.0	94.1
1.00	134.2	136.6	136.2	134.7	137.7	135.2

Regression Output:	RUN 1
Constant	−0.598425
Std Err of Y Est	4.9928681
R Squared	0.9919644
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	135.31659
Std Err of Coef.	5.4500162

Regression Output:	RUN 3
Constant	−1.889319
Std Err of Y Est	3.4603747
R Squared	0.9962069
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	136.87744
Std Err of Coef.	3.7771846

Regression Output:	RUN 2
Constant	−1.144425
Std Err of Y Est	4.2439908
R Squared	0.9944618
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	138.79659
Std Err of Coef.	4.6322162

Regression Output:	3 STD RUNS COMBINED
Constant	−1.144056
Std Err of Y Est	3.8757308
R Squared	0.9939996
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	136.99687
Std Err of Coef.	2.4425196

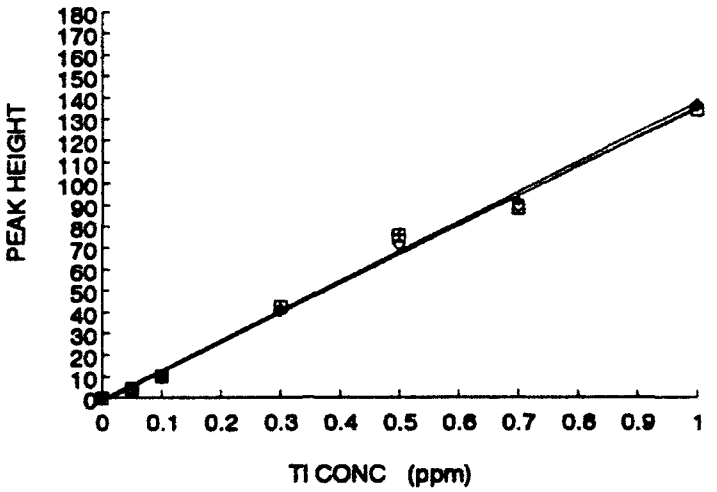
FILE A_B_K1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/12/93

SAMPLE: KIDNEY

GROUPS: DMPS (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE TI CONC (ppm)
TB 1	40.5	41.5			41.0	0.31
TB 2	42.1	41.3			41.7	0.31
TB 3	36.0	38.1			37.1	0.28
TB 4	73.0	72.8			72.9	0.54
TB 5	72.6	75.2			73.9	0.56
TB 6	70.0	70.8			70.4	0.52
TB 7	61.8	64.8			63.3	0.47
TB 8	66.6	67.6			67.1	0.50
TB 9	60.4	57.6			59.0	0.44
TB 10	60.2	56.8			58.5	0.44
CB 1	69.4	70.6			70.0	0.52
CB 2	62.0	64.6			63.3	0.47
CB 3	71.8	69.8			70.8	0.53
CB 4	64.4	61.8			63.1	0.47
CB 5	71.4	62.6	68.6		67.5	0.50
CB 6	62.5	66.2			64.4	0.48
CB 7	66.8	59.2	61.5		62.5	0.46

TI CONC = (y - b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/11/93

FILE: A_B_K2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: KIDNEY
DMPS

DATE ANALYZED: 2/12/93

PATH: c:\data\lotus2.3
a:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	Tl CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A – B			D x E		F x G / C	
TB 1	72.0917	71.8725	0.2192	5.0	8	40	0.31	56.14	
TB 2	71.6856	71.4463	0.2395	5.0	8	40	0.31	52.23	
TB 3	78.6258	78.4061	0.2197	5.0	8	40	0.28	50.76	
TB 4	81.1039	80.8467	0.2572	5.0	8	40	0.54	84.06	
TB 5	78.1013	77.8731	0.2282	5.0	8	40	0.55	96.02	
TB 6	79.2751	79.0442	0.2309	5.0	8	40	0.52	90.47	
TB 7	78.8299	78.5756	0.2543	5.0	8	40	0.47	73.99	
TB 8	79.6965	79.6389	0.2596	5.0	8	40	0.50	78.76	
TB 9	72.4406	72.1998	0.2408	5.0	8	40	0.44	70.30	
TB 10	72.4942	72.2683	0.2259	5.0	8	40	0.44	77.09	
CB 1	78.9080	78.6991	0.2089	5.0	8	40	0.52	86.95	
CB 2	78.0446	77.7831	0.2615	5.0	8	40	0.47	71.95	
CB 3	81.7529	81.5207	0.2322	5.0	8	40	0.53	90.47	DIED DAY 5
CB 4	78.1559	77.9040	0.2519	5.0	8	40	0.47	74.47	
CB 5	72.0197	71.7783	0.2414	5.0	8	40	0.50	83.07	
CB 6	72.1473	71.9136	0.2337	5.0	8	40	0.48	81.83	
CB 7	81.6231	81.3902	0.2329	5.0	8	40	0.46	79.79	
MEAN			0.2396						

FILE A_C_K1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/13/93

SAMPLE: KIDNEY

GROUPS: PB + DMPS (TX & NO TX)

RUN 1 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	4.1					4.1
0.10	10.3					10.3
0.30	43.7					43.7
0.50	75.0					75.0
0.70	90.6					90.6
1.00	138.6					138.6

RUN 2 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	4.0					4.0
0.1	10.1					10.1
0.3	44.8					44.8
0.5	81.2					81.2
0.7	92.2					92.2
1.00	138.8					138.8

RUN 3 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	3.7					3.7
0.1	11.6					11.6
0.3	46.4					46.4
0.5	78.4					78.4
0.7	97.4					97.4
1.00	145.4					145.4

FILE A_C_K1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/13/93

SAMPLE: KIDNEY

GROUPS: PB + DMPS (TX & NO TX)

TI STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	−0.9	−0.3	−0.8
0.05	4.1	4.0	3.7	6.1	6.8	6.5
0.10	10.3	10.1	11.6	13.0	13.8	13.8
0.30	43.7	44.8	46.4	40.8	42.0	43.2
0.50	75.0	81.2	78.4	68.6	70.1	72.5
0.70	90.6	92.2	97.4	96.5	98.2	101.8
1.00	138.6	138.8	145.4	138.2	140.5	145.8

Regression Output:	RUN 1
Constant	−0.885872
Std Err of Y Est	4.3623581
R Squared	0.9941712
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	139.05702
Std Err of Coef.	4.7617479

Regression Output:	RUN 3
Constant	−0.821446
Std Err of Y Est	3.9656572
R Squared	0.9956633
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	146.66042
Std Err of Coef.	4.3286184

Regression Output:	RUN 2
Constant	−0.257319
Std Err of Y Est	6.1989767
R Squared	0.9885708
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	140.71744
Std Err of Coef.	6.7665157

Regression Output:	3 STD RUNS COMBINED
Constant	−0.654679
Std Err of Y Est	4.7198744
R Squared	0.9917487
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	142.14466
Std Err of Coef.	2.9745063

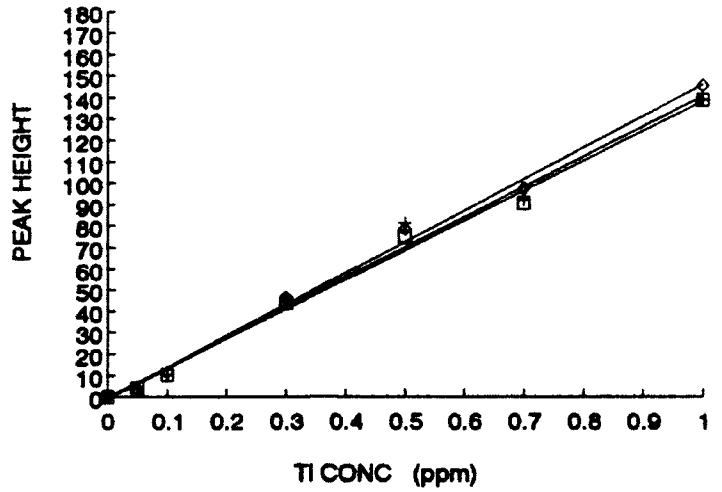
FILE A_C_K1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/13/93

SAMPLE: KIDNEY

GROUPS: PB + DMPS (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE Tl CONC (ppm)
TC 1	70.0	71.2			70.6	0.50
TC 2	72.2	70.6			71.4	0.51
TC 3	73.0	72.6			72.8	0.52
TC 4	48.6	53.4			51.0	0.36
TC 5	51.2	53.6			52.4	0.37
TC 6	67.8	69.8			68.8	0.49
TC 7	63.2	66.4			64.8	0.46
TC 8	66.0	63.4			64.7	0.46
TC 9	48.2	56.8			52.5	0.37
TC 10	66.0	66.2			66.1	0.47
CC 1	48.2	52.2			50.2	0.36
CC 2	69.4	69.0			69.2	0.49
CC 3	56.0	60.6			58.3	0.41
CC 4	67.2	68.8			68.0	0.48
CC 5	71.0	77.4			74.2	0.53
CC 6	62.0	64.0			63.0	0.45
CC 7	65.8	65.6			65.7	0.47

Tl CONC = (y - b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/12/93

FILE: A_C_K2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: KIDNEY
PB + DMPS

DATE ANALYZED: 2/13/93

PATH: c:\data\lotus2.3
a:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	Tl CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A – B			D x E		F x G / C	
TC 1	60.2189	59.9462	0.2727	5	4	20	0.50	36.76	
TC 2	60.2214	59.9494	0.2720	5	4	20	0.51	37.27	
TC 3	58.5980	58.3229	0.2751	5	4	20	0.52	37.57	
TC 4	49.6324	49.3842	0.2482	5	4	20	0.36	29.28	
TC 5	61.9322	61.6776	0.2546	5	4	20	0.37	29.32	
TC 6	49.6325	49.3839	0.2486	5	4	20	0.49	39.31	
TC 7	61.9019	61.6684	0.2335	5	4	20	0.46	39.44	
TC 8	60.2606	59.9943	0.2663	5	4	20	0.46	34.53	
TC 9	60.4931	60.2184	0.2747	5	4	20	0.37	27.23	
TC 10	61.4574	61.1937	0.2637	5	4	20	0.47	35.62	
CC 1	62.3979	62.1389	0.2590	5	8	40	0.36	55.25	
CC 2	62.9293	62.6886	0.2407	5	8	40	0.49	81.67	
CC 3	61.8063	61.5462	0.2591	5	8	40	0.41	64.03	
CC 4	49.3142	49.1007	0.2135	5	8	40	0.48	90.49	DIED DAY 5
CC 5	56.8607	56.6325	0.2282	5	8	40	0.53	92.31	DIED DAY 4
CC 6	50.2994	50.0381	0.2613	5	8	40	0.45	68.55	
CC 7	62.3352	62.0561	0.2791	5	8	40	0.47	66.90	
MEAN			0.2559						

LIVER

FILE A_A_L1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/14/93

SAMPLE: LIVER

GROUPS: PB (TX & NO TX)

RUN 1 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.4					5.4
0.10	15.1					15.1
0.30	46.9					46.9
0.50	79.4					79.4
0.70	104.4					104.4
1.00	152.1	149.2				150.7

RUN 2 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.4					5.4
0.1	15.2					15.2
0.3	44.3					44.3
0.5	81.6					81.6
0.7	105.0					105.0
1.00	150.2	151.6				150.9

RUN 3 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.1					5.1
0.1	12.7					12.7
0.3	45.5					45.5
0.5	76.6	76.0				76.3
0.7	102.0					102.0
1.00	148.5	147.7				148.1

FILE A_A_L1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/14/93

SAMPLE: LIVER

GROUPS: PB (TX & NO TX)

TI STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	0.1	−0.2	−0.8
0.05	5.4	5.4	5.1	7.6	7.4	6.6
0.10	15.1	15.2	12.7	15.2	15.0	14.1
0.30	46.9	44.3	45.5	45.5	45.5	43.9
0.50	79.4	81.6	76.3	75.8	76.0	73.8
0.70	104.4	106.0	102.0	106.1	106.5	103.7
1.00	150.7	150.9	148.1	151.6	152.2	148.4

Regression Output:	RUN 1
Constant	0.0538936
Std Err of Y Est	2.1717750
R Squared	0.9987772
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	151.49914
Std Err of Coef.	2.3706090

Regression Output:	RUN 3
Constant	−0.844936
Std Err of Y Est	1.8156932
R Squared	0.9991195
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	149.28851
Std Err of Coef.	1.9819288

Regression Output:	RUN 2
Constant	−0.224680
Std Err of Y Est	2.8561175
R Squared	0.9979067
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	152.44255
Std Err of Coef.	3.1208801

Regression Output:	3 STD RUNS COMBINED
Constant	−0.338574
Std Err of Y Est	2.2948829
R Squared	0.9982818
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	151.07673
Std Err of Coef.	1.4462564

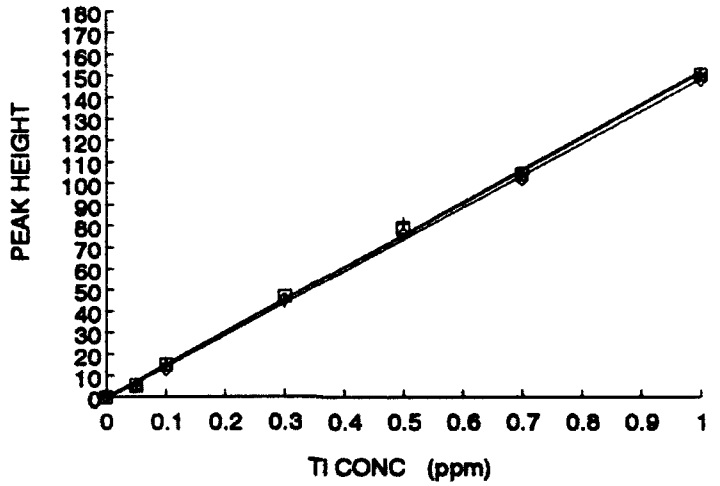
FILE A_A_L1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/14/83

SAMPLE: LIVER

GROUPS: PB (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE Tl CONC (ppm)
TA 1	88.4	86.8			87.6	0.58
TA 2	84.8	83.6			84.2	0.56
TA 3	75.4	75.2			75.3	0.50
TA 4	73.2	68.8			71.0	0.47
TA 5	65.8	67.0			66.4	0.44
TA 6	78.8	77.6			78.2	0.52
TA 7	78.0	78.8			78.4	0.52
TA 8	77.2	79.2			78.2	0.52
TA 9	65.4	63.6			64.5	0.43
TA 10	77.0	79.0			78.0	0.52
CA 1	76.4	75.4			75.9	0.50
CA 2	62.2	65.6			63.9	0.43
CA 3	79.0	77.8			78.4	0.52
CA 4	59.6	65.6			62.6	0.42
CA 5	74.4	77.8			76.1	0.51
CA 6	96.8	98.0			97.4	0.65
CA 7	81.4	83.0			82.2	0.55

Tl CONC = (y - b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/13/93

FILE: A_A_L2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: LIVER
PB

DATE ANALYZED: 2/14/93

PATH: c:\data\lotus2.3
a:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	TI CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A – B			D x E		F x G / C	
TA 1	62.0709	61.5618	0.5091	5	1	5	0.56	5.72	
TA 2	49.2671	48.7378	0.5293	5	1	5	0.56	5.29	
TA 3	59.0566	58.6023	0.4543	5	1	5	0.50	5.51	
TA 4	58.8060	58.3128	0.4932	5	1	5	0.47	4.79	
TA 5	62.2119	61.6954	0.5165	5	1	5	0.44	4.28	
TA 6	63.0479	62.5243	0.5236	5	1	5	0.52	4.96	
TA 7	62.6882	62.1511	0.5371	5	1	5	0.52	4.85	
TA 8	61.7239	61.2282	0.4957	5	1	5	0.52	5.24	
TA 9	61.7809	61.3148	0.4661	5	1	5	0.43	4.60	
TA 10	59.5346	59.0297	0.5049	5	1	5	0.52	5.14	
CA 1	62.5622	62.0249	0.5373	5	2	10	0.50	9.39	
CA 2	58.5578	58.0315	0.5263	5	2	10	0.43	8.06	
CA 3	60.3988	59.8217	0.5771	5	2	10	0.52	9.03	
CA 4	62.4806	61.9734	0.5074	5	2	10	0.42	8.21	
CA 5	56.3914	55.8974	0.4940	5	2	10	0.51	10.24	
CA 6	62.8578	62.3449	0.5127	5	2	10	0.65	12.62	DIED DAY 4
CA 7	62.2272	61.6924	0.5348	5	2	10	0.55	10.22	
MEAN			0.5129						

FILE A_B_L1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/15/93

SAMPLE: LIVER

GROUPS: DMPS (TX & NO TX)

RUN 1 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.7					5.7
0.10	13.5					13.5
0.30	57.8					57.8
0.50	76.0					76.0
0.70	103.4					103.4
1.00	130.2	124.8				127.5

RUN 2 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.4					5.4
0.1	12.5					12.5
0.3	53.3					53.3
0.5	72.6					72.6
0.7	105.6					105.6
1.00	137.2	136.8				137.0

RUN 3 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.0					5.0
0.1	6.6	8.7				7.7
0.3	56.7					56.7
0.5	67.0	68.0				67.5
0.7	96.4					96.4
1.00	125.4	132.7				129.1

FILE A_B_L1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/15/93

SAMPLE: LIVER

GROUPS: DMPS (TX & NO TX)

TI STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	4.8	1.8	1.8
0.05	5.7	5.4	5.0	11.2	8.8	8.2
0.10	13.5	12.5	7.7	17.8	15.9	14.9
0.30	57.8	53.3	56.7	44.4	44.1	41.4
0.50	76.0	72.6	67.5	71.0	72.3	67.8
0.70	103.4	106.8	96.4	97.6	100.6	94.3
1.00	127.8	137.0	129.1	137.4	142.9	134.1

Regression Output:	RUN 1
Constant	4.5395744
Std Err of Y Est	9.0180858
R Squared	0.9732023
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	132.87659
Std Err of Coef.	9.8437244

Regression Output:	RUN 3
Constant	1.6220425
Std Err of Y Est	8.1270744
R Squared	0.9780585
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	132.43234
Std Err of Coef.	8.8711377

Regression Output:	RUN 2
Constant	1.7714893
Std Err of Y Est	5.8491825
R Squared	0.9896707
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	141.13191
Std Err of Coef.	6.3846965

Regression Output:	3 STD RUNS COMBINED
Constant	2.8443687
Std Err of Y Est	7.2488638
R Squared	0.9788533
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	136.48028
Std Err of Coef.	4.5683727

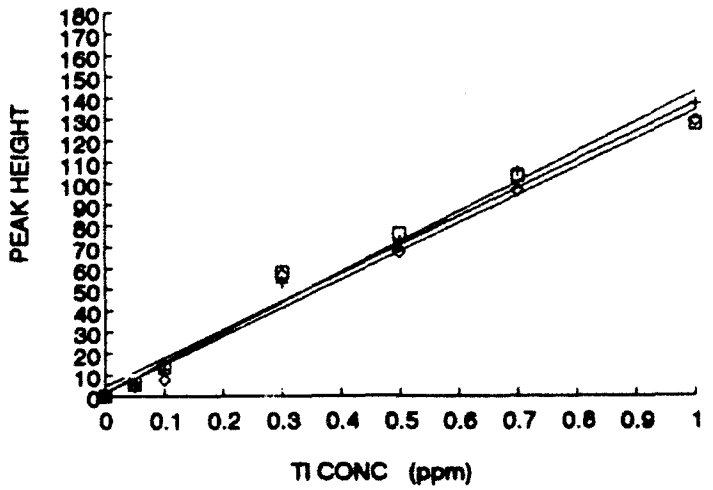
FILE A_B_L1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/18/93

SAMPLE: LIVER

GROUPS: DMPS (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE TI CONC (ppm)
TB 1	72.6	70.0			71.3	0.51
TB 2	72.0	70.2			71.1	0.51
TB 3	61.4	63.0			62.2	0.44
TB 4	59.8	61.8			60.8	0.43
TB 5	60.0	59.4	57.8		62.1	0.44
TB 6	63.4	58.4			60.9	0.43
TB 7	66.6	63.6			66.1	0.47
TB 8	60.8	59.2			62.0	0.59
TB 9	63.8	57.0	58.2		59.7	0.42
TB 10	67.0	65.4			66.2	0.47
CB 1	75.4	74.0			74.7	0.53
CB 2	62.0	60.0			61.0	0.43
CB 3	93.2	91.6			92.4	0.66
CB 4	68.0	66.4			67.2	0.48
CB 5	60.0	61.0			60.5	0.43
CB 6	64.2	64.8			64.5	0.46
CB 7	66.6	64.6			65.6	0.46

TI CONC = (y - b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/14/93

FILE: A_B_L2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: LIVER
DMPS

DATE ANALYZED: 2/15/93

PATH: c:\data\lotus2.3
a:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	Tl CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A – B			D x E		F x G / C	
TB 1	82.0178	81.5219	0.4959	5.0	2	10	0.51	10.22	
TB 2	79.5736	79.0440	0.5296	5.0	2	10	0.51	9.54	
TB 3	81.9104	81.3898	0.5206	5.0	2	10	0.44	8.44	
TB 4	78.4223	77.8730	0.5493	5.0	2	10	0.43	7.81	
TB 5	72.3991	71.9139	0.4852	5.0	2	10	0.44	9.04	
TB 6	72.7214	72.1994	0.5220	5.0	2	10	0.43	8.24	
TB 7	81.4201	80.8463	0.5738	5.0	2	10	0.47	8.18	
TB 8	72.2903	71.7781	0.5122	5.0	2	10	0.59	11.44	
TB 9	72.4248	71.8723	0.5525	5.0	2	10	0.42	7.62	
TB 10	80.1386	79.6386	0.5000	5.0	2	10	0.47	9.37	
CB 1	78.9164	78.4059	0.5105	5.0	2	10	0.53	10.42	
CB 2	79.0696	78.5754	0.4944	5.0	2	10	0.43	8.71	
CB 3	78.3197	77.7832	0.5365	5.0	2	10	0.66	12.36	DIED DAY 5
CB 4	78.4263	77.9037	0.5226	5.0	2	10	0.48	9.12	
CB 5	79.1204	78.6210	0.4994	5.0	2	10	0.43	8.55	
CB 6	71.9211	71.4507	0.4704	5.0	2	10	0.46	9.71	
CB 7	72.7093	72.2379	0.4714	5.0	2	10	0.46	9.86	
MEAN			0.5145						

FILE A_C_L1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/16/93

SAMPLE: LIVER

GROUPS: PB + DMPS (TX & NO TX)

RUN 1 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.0	4.0				4.5
0.10	13.8					13.8
0.30	61.8					61.8
0.50	93.6					93.6
0.70	136.6					136.6
1.00	149.8	149.0				149.4

RUN 2 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.0					5.0
0.1	14.6					14.6
0.3	59.3					59.3
0.5	94.2					94.2
0.7	127.8					127.8
1.00	157.0	160.8				158.9

RUN 3 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	4.8					4.8
0.1	13.4					13.4
0.3	59.8					59.8
0.5	88.2					88.2
0.7	120.4					120.4
1.00	159.0					159.0

FILE A_C_L1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/16/93

SAMPLE: LIVER

GROUPS: PB + DMPS (TX & NO TX)

Tl STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	3.5	2.1	1.3
0.05	4.5	5.0	4.8	11.7	10.5	9.5
0.10	13.8	14.6	13.4	19.9	18.9	17.7
0.30	61.8	59.3	59.6	52.8	52.5	50.7
0.50	93.6	94.2	88.2	85.6	86.1	83.6
0.70	136.6	127.8	120.4	118.5	119.6	116.6
1.00	149.4	158.9	156.0	167.8	170.0	166.0

Regression Output:	RUN 1
Constant	3.4536170
Std Err of Y Est	13.506045
R Squared	0.9613230
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	164.34893
Std Err of Coef.	14.742573

Regression Output:	RUN 3
Constant	1.2805957
Std Err of Y Est	6.4257972
R Squared	0.9910123
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	164.69276
Std Err of Coef.	7.0141023

Regression Output:	RUN 2
Constant	2.1340425
Std Err of Y Est	8.4384227
R Squared	0.9851701
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	167.87234
Std Err of Coef.	9.2109911

Regression Output:	3 STD RUNS COMBINED
Constant	2.2894184
Std Err of Y Est	8.8867211
R Squared	0.9787404
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	165.63801
Std Err of Coef.	5.0004898

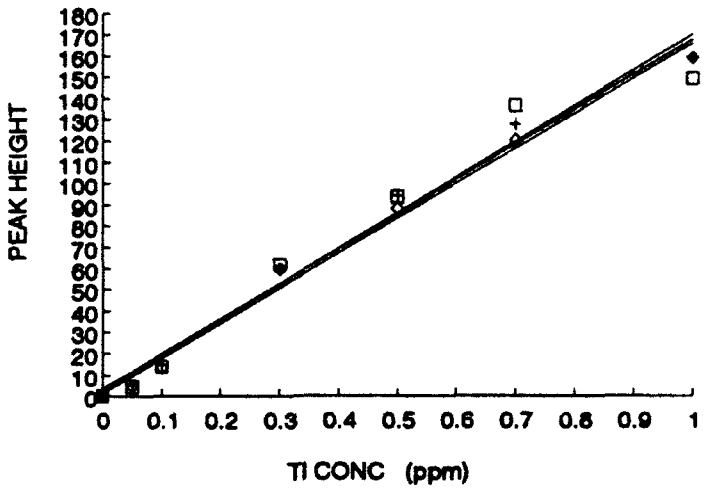
FILE A_C_L1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/16/93

SAMPLE: LIVER

GROUPS: PB + DMPS (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE Tl CONC (ppm)
TC 1	95.8	95.2			95.4	0.56
TC 2	90.6	93.6			92.1	0.54
TC 3	97.0	99.0			98.0	0.58
TC 4	89.6	89.0			89.3	0.53
TC 5	96.0	98.8			97.4	0.57
TC 6	126.0	121.2			123.6	0.73
TC 7	108.0	107.2			107.6	0.64
TC 8	91.0	102.8			96.9	0.57
TC 9	110.8	111.0			110.9	0.66
TC 10	109.0	103.0			106.0	0.63
CC 1	90.0	92.6			91.3	0.54
CC 2	91.2	88.4			89.8	0.53
CC 3	108.0	105.6			106.8	0.63
CC 4	124.4	126.6			125.5	0.74
CC 5	120.0	119.8			119.9	0.71
CC 6	104.6	98.4			101.5	0.60
CC 7	99.4	100.0			99.7	0.59

Tl CONC = (y - b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y – INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/15/93

FILE: A_C_L2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: LIVER
PB + DMPS

DATE ANALYZED: 2/16/93

PATH: c:\data\lotus2.3
a:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	Tl CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A - B			D x E		F x G / C	
TC 1	81.5266	81.0346	0.4920	5.0	1	5	0.56	5.71	
TC 2	72.3098	71.7951	0.5147	5.0	1	5	0.54	5.27	
TC 3	78.9341	78.3994	0.5347	5.0	1	5	0.58	5.40	
TC 4	78.6052	78.1292	0.4760	5.0	1	5	0.53	5.52	
TC 5	78.6086	78.0603	0.5483	5.0	1	5	0.57	5.24	
TC 6	78.9908	78.5007	0.4901	5.0	1	5	0.73	7.47	
TC 7	78.5785	78.0306	0.5479	5.0	1	5	0.64	5.80	
TC 8	78.8097	78.3346	0.4751	5.0	1	5	0.57	6.01	
TC 9	78.2641	77.7819	0.4822	5.0	1	5	0.66	6.80	
TC 10	72.4319	71.9302	0.5017	5.0	1	5	0.63	6.24	
CC 1	78.3580	77.8643	0.4917	5.0	2	10	0.54	10.93	
CC 2	78.7411	78.2775	0.4636	5.0	2	10	0.53	11.40	
CC 3	72.7781	72.1753	0.6028	5.0	2	10	0.63	10.47	
CC 4	72.8383	72.2390	0.5993	5.0	2	10	0.74	12.41	DIED DAY 5
CC 5	79.2926	78.7149	0.5777	5.0	2	10	0.71	12.29	DIED DAY 4
CC 6	79.5542	78.9623	0.5919	5.0	2	10	0.60	10.12	
CC 7	71.8695	71.3758	0.4937	5.0	2	10	0.59	11.91	
MEAN			0.5226						

HEART

FILE A_A_H1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/17/93

SAMPLE: HEART

GROUPS: PB (TX & NO TX)

RUN 1 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.0					5.0
0.10	13.2					13.2
0.30	59.6					59.6
0.50	89.0					89.0
0.70	121.6					121.6
1.00	170.4	165.4				167.9

RUN 2 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	4.6					4.6
0.1	13.3					13.3
0.3	57.7					57.7
0.5	79.6					79.6
0.7	118.0					118.0
1.00	154.0	162.0				158.0

RUN 3 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	4.7					4.7
0.1	14.7					14.7
0.3	58.6					58.6
0.5	84.6					84.6
0.7	114.8					114.8
1.00	156.2	160.0				158.1

FILE A_A_H1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/17/83

SAMPLE: HEART

GROUPS: PB (TX & NO TX)

Tl STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	0.1	0.2	1.2
0.05	5.0	4.6	4.7	6.7	6.3	9.3
0.10	13.2	13.3	14.7	17.3	16.4	17.3
0.30	59.6	57.7	58.6	61.7	48.9	49.6
0.50	89.0	79.6	84.6	86.1	81.3	81.6
0.70	121.6	118.0	114.6	120.4	113.7	114.0
1.00	167.9	158.0	158.1	172.0	162.3	162.3

Regression Output:	RUN 1
Constant	0.1297446
Std Err of Y Est	4.9021295
R Squared	0.9951755
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	171.84585
Std Err of Coef.	5.3509373

Regression Output:	RUN 3
Constant	1.2407659
Std Err of Y Est	5.2480535
R Squared	0.9937146
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	161.06212
Std Err of Coef.	5.7285320

Regression Output:	RUN 2
Constant	0.2417872
Std Err of Y Est	5.2304622
R Squared	0.9935974
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	162.07829
Std Err of Coef.	5.8184856

Regression Output:	3 RUNS COMBINED
Constant	0.5374328
Std Err of Y Est	5.1858617
R Squared	0.9926011
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	164.89546
Std Err of Coef.	3.2680466

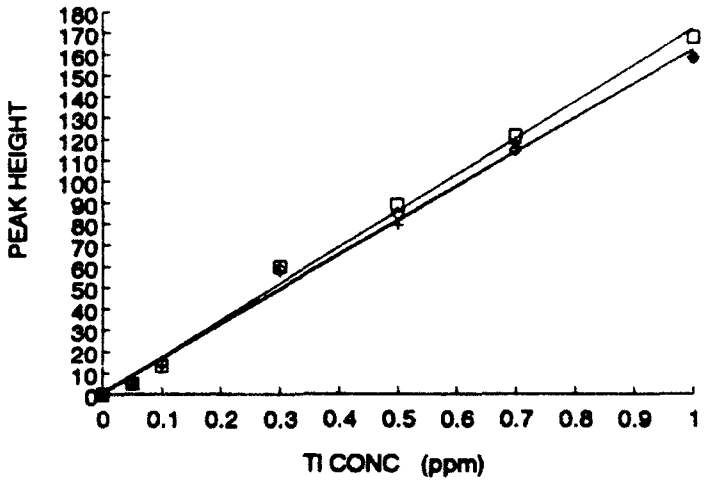
FILE A_A_H1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/17/93

SAMPLE: HEART

GROUPS: PB (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE Tl CONC (ppm)
TA 1	114.0	114.2			114.1	0.89
TA 2	107.4	112.0			109.7	0.86
TA 3	87.4	79.0			83.2	0.50
TA 4	78.0	84.4			81.2	0.49
TA 5	89.2	79.8			84.5	0.51
TA 6	112.2	105.4			108.8	0.86
TA 7	101.4	97.4			99.4	0.80
TA 8	100.8	96.6			98.7	0.59
TA 9	103.2	100.6			101.9	0.81
TA 10	103.6	100.2	104		102.6	0.82
CA 1	86.0	84.0			85.0	0.51
CA 2	114.4	110.8			112.6	0.88
CA 3	100.8	90.4			95.6	0.58
CA 4	87.6	72.0	80.4		80.0	0.48
CA 5	84.6	80.0			82.3	0.50
CA 6	127.4	125.2			126.3	0.76
CA 7	110.6	100.8			105.7	0.64

Tl CONC = (y – b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y – INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/16/93

FILE: A_A_H2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: HEART
PB

DATE ANALYZED: 2/17/93

PATH: c:\data\lotus2.3
e:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g)	BEAKER TARE WT (g)	NET WT SAMPLE (g)	DILUTION FACTOR (sample extracted into 5 ml MIBK)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve)	TOTAL DILUTION FACTOR	SAMPLE CONC (ppm)	TI CONC ug Tl/g tissue (wet wt)	COMMENTS
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(I-)	
FORMULA			A - B			D x E		F x G / C	
TA 1	82.4487	81.9824	0.4663	5.0	2	10	0.69	14.76	
TA 2	49.9643	49.4822	0.4821	5.0	2	10	0.68	13.72	
TA 3	85.8116	85.2908	0.5208	5.0	2	10	0.50	9.62	
TA 4	81.8129	81.2947	0.5182	5.0	2	10	0.49	9.43	
TA 5	80.5026	79.9513	0.5513	5.0	2	10	0.51	9.23	
TA 6	77.8517	77.3171	0.5346	5.0	2	10	0.66	12.27	
TA 7	79.2121	78.7236	0.4885	5.0	2	10	0.60	12.27	
TA 8	72.5254	72.0662	0.4592	5.0	2	10	0.59	12.96	
TA 9	72.1018	71.5815	0.5203	5.0	2	10	0.61	11.81	
TA 10	80.4388	79.8923	0.5465	5.0	2	10	0.62	11.32	
CA 1	79.2217	78.6964	0.5253	5.0	4	20	0.51	19.49	
CA 2	77.4592	76.9130	0.5462	5.0	4	20	0.68	24.87	
CA 3	79.4523	78.9879	0.4644	5.0	4	20	0.56	24.81	
CA 4	72.4809	71.9957	0.4852	5.0	4	20	0.48	19.85	
CA 5	78.2175	77.7187	0.4988	5.0	4	20	0.50	19.87	
CA 6	78.8401	78.3325	0.5076	5.0	4	20	0.76	30.03	DIED DAY 4
CA 7	78.9463	78.4483	0.4980	5.0	4	20	0.64	25.80	
MEAN			0.5087						

FILE A_B_H1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/18/93

SAMPLE: HEART

GROUPS: DMPS (TX & NO TX)

RUN 1 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.9					5.9
0.10	16.3					16.3
0.30	63.8					63.8
0.50	89.2					89.2
0.70	112.8					112.8
1.00	142.4					142.4

RUN 2 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	6.4					6.4
0.1	15.5					15.5
0.3	62.1					62.1
0.5	86.8					86.8
0.7	113.0					113.0
1.00	140.4	151.0	145.0			145.5

RUN 3 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	6.0					6.0
0.1	14.4					14.4
0.3	65.0					65.0
0.5	84.0					84.0
0.7	114.0					114.0
1.00	147.4	142.8				145.1

FILE A_B_H1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/18/93

SAMPLE: HEART

GROUPS: DMPS (TX & NO TX)

TI STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	5.5	4.5	4.4
0.05	5.9	6.4	6.0	12.9	12.0	11.9
0.10	16.3	15.5	14.4	20.3	19.5	19.4
0.30	63.6	62.1	65.0	48.8	48.5	49.4
0.50	89.2	86.8	84.0	79.4	79.5	79.4
0.70	112.8	113.0	114.0	109.0	109.6	109.4
1.00	142.4	145.5	145.1	153.3	154.6	154.5

Regression Output:	RUN 1
Constant	5.4786106
Std Err of Y Est	10.137846
R Squared	0.9727569
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	147.86808
Std Err of Coef.	11.066003

Regression Output:	RUN 3
Constant	4.4153617
Std Err of Y Est	9.5008764
R Squared	0.9766661
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	150.03489
Std Err of Coef.	10.370716

Regression Output:	RUN 2
Constant	4.5094539
Std Err of Y Est	8.8429676
R Squared	0.9806249
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	150.07829
Std Err of Coef.	9.4341537

Regression Output:	3 STD RUNS COMBINED
Constant	4.8007754
Std Err of Y Est	8.4029960
R Squared	0.9769823
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	149.32709
Std Err of Coef.	5.2956419

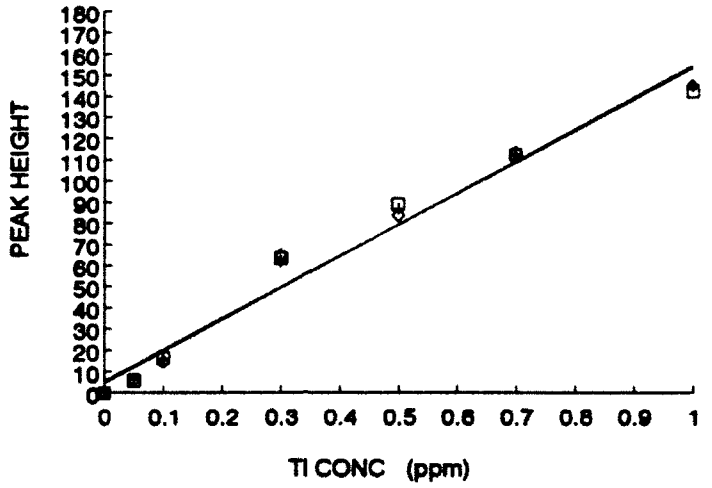
FILE A_B_H1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/18/93

SAMPLE: HEART

GROUPS: DMPS (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE Tl CONC (ppm)
TB 1	87.2	88.2			87.7	0.56
TB 2	84.6	81.2			82.9	0.52
TB 3	61.6	63.4			62.5	0.39
TB 4	71.2	76.8			74.0	0.46
TB 5	79.6	79.4			79.5	0.50
TB 6	91.8	92.0			91.9	0.58
TB 7	96.0	96.2			96.6	0.61
TB 8	79.2	79.0			79.1	0.50
TB 9	83.0	84.0			83.5	0.53
TB 10	82.2	82.4			82.3	0.52
CB 1	86.6	87.6			87.1	0.55
CB 2	80.4	80.0			80.2	0.50
CB 3	115.6	111.6			113.6	0.73
CB 4	78.6	78.4			78.5	0.49
CB 5	73.4	73.0			73.2	0.46
CB 6	86.8	85.4			86.1	0.54
CB 7	85.2	76.0	81.8		80.7	0.51

Tl CONC = (y - b) / m WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/17/93

FILE: A_B_H2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: HEART
DMPS

DATE ANALYZED: 2/18/93

PATH: c:\data\lotus2.3
e:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	Tl CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A – B			D x E		F x G / C	
TB 1	79.3239	78.8051	0.5188	5.0	4	20	0.56	21.40	
TB 2	72.3101	71.8398	0.4703	5.0	4	20	0.52	22.24	
TB 3	72.1958	71.7147	0.4811	5.0	4	20	0.39	16.06	
TB 4	72.6174	72.1182	0.4992	5.0	4	20	0.46	18.57	
TB 5	78.2426	77.7101	0.5325	5.0	4	20	0.50	18.79	
TB 6	81.4879	81.0158	0.4721	5.0	4	20	0.58	24.71	
TB 7	81.9856	81.5062	0.4794	5.0	4	20	0.61	25.37	
TB 8	78.3337	77.8291	0.5046	5.0	4	20	0.50	19.72	
TB 9	78.2850	77.8069	0.4781	5.0	4	20	0.53	22.14	
TB 10	79.1022	78.5998	0.5024	5.0	4	20	0.52	20.66	
CB 1	81.2651	80.7728	0.4923	5.0	4	20	0.55	22.39	
CB 2	78.8498	78.3293	0.5205	5.0	4	20	0.50	19.41	
CB 3	53.4394	52.9463	0.4931	5.0	4	20	0.73	29.55	DIED DAY 5
CB 4	61.8912	61.1793	0.5119	5.0	4	20	0.49	19.28	
CB 5	50.5073	50.0130	0.4943	5.0	4	20	0.46	18.53	
CB 6	55.8795	55.3918	0.4877	5.0	4	20	0.54	22.33	
CB 7	61.7979	61.2955	0.5023	5.0	4	20	0.51	20.23	
MEAN			0.4964						

FILE A_C_H1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/22/93

SAMPLE: HEART

GROUPS: PB + DMPS (TX & NO TX)

RUN 1 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	7.3					7.3
0.10	15.5					15.5
0.30	51.6	52.0				51.8
0.50	81.8					81.8
0.70	111.4					111.4
1.00	143.0					143.0

RUN 2 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	7.4					7.4
0.1	17.6					17.6
0.3	53.5					53.5
0.5	80.0					80.0
0.7	107.4					107.4
1.00	132.2					132.2

RUN 3 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	6.8					6.8
0.1	18.1					18.1
0.3	49.9					49.9
0.5	81.8					81.8
0.7	106.6					106.6
1.00	128.2					128.2

FILE A_C_H1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/22/93

SAMPLE: HEART

GROUPS: PB + DMPS (TX & NO TX)

Tl STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	2.8	5.1	5.1
0.05	7.3	7.4	6.8	10.2	11.9	11.8
0.10	15.5	17.6	16.1	17.6	18.8	18.5
0.30	51.8	53.5	49.9	47.1	46.1	45.4
0.50	81.8	80.0	81.8	76.6	73.5	72.2
0.70	111.4	107.4	106.6	106.1	100.9	99.1
1.00	143.0	132.2	128.2	150.4	141.9	139.3

Regression Output:	RUN 1
Constant	2.8356574
Std Err of Y Est	5.5196995
R Squared	0.9917299
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	147.52765
Std Err of Coef.	8.0249389

Regression Output:	RUN 3
Constant	5.0942127
Std Err of Y Est	8.2996330
R Squared	0.9777349
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	134.24170
Std Err of Coef.	9.0564946

Regression Output:	RUN 2
Constant	5.0864255
Std Err of Y Est	7.5006841
R Squared	0.9824169
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	136.84340
Std Err of Coef.	8.1872572

Regression Output:	3 STD RUNS COMBINED
Constant	4.3321985
Std Err of Y Est	8.8402564
R Squared	0.9821993
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	139.53758
Std Err of Coef.	4.3107897

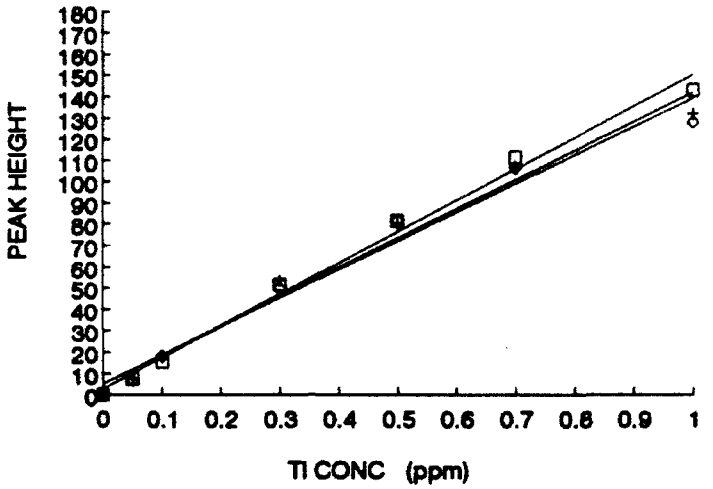
FILE A_C_H1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/22/93

SAMPLE: HEART

GROUPS: PB + DMPS (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE TI CONC (ppm)
TC 1	68.4	78.0	75.0		73.8	0.50
TC 2	80.0	84.8			82.4	0.56
TC 3	98.8	111.4	95.8		102.0	0.70
TC 4	74.8	90.2	86.2		77.1	0.52
TC 5	68.8	76.8			71.8	0.48
TC 6	76.4	76.6			76.5	0.52
TC 7	58.2	62.6			60.4	0.40
TC 8	78.0	84.2	82.8		88.3	0.46
TC 9	63.4	62.2			62.8	0.42
TC 10	75.0	81.0	82.6		88.2	0.44
CC 1	80.2	80.4			80.3	0.54
CC 2	84.0	83.8			83.9	0.57
CC 3	71.0	68.0			69.5	0.47
CC 4	106.8	101.8			104.2	0.72
CC 5	84.4	89.4			86.9	0.59
CC 6	83.2	85.8			84.5	0.57
CC 7	78.4	80.2			79.3	0.54

TI CONC = (y - b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/16/93

FILE: A_C_H2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: HEART
PB + DMPS

DATE ANALYZED: 2/22/93

PATH: c:\data\lotus2.3
a:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	Tl CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A - B			D x E		F x G / C	
TC 1	83.2378	82.7453	0.4925	5.0	2	10	0.50	10.11	
TC 2	57.0579	56.5648	0.4931	5.0	2	10	0.56	11.35	
TC 3	60.9289	60.4109	0.5180	5.0	2	10	0.70	13.51	
TC 4	49.5106	49.0236	0.4870	5.0	2	10	0.52	10.70	
TC 5	61.8456	61.3347	0.5111	5.0	2	10	0.46	9.46	
TC 6	60.6417	60.1371	0.5046	5.0	2	10	0.52	10.25	
TC 7	63.0422	62.5253	0.5169	5.0	2	10	0.40	7.77	
TC 8	58.9941	58.4633	0.5308	5.0	2	10	0.46	8.64	
TC 9	60.5684	60.0878	0.4786	5.0	2	10	0.42	8.78	
TC 10	60.6008	60.1264	0.4744	5.0	2	10	0.44	9.35	
CC 1	49.0113	48.5264	0.4849	5.0	4	20	0.54	22.46	
CC 2	60.3099	59.7826	0.5273	5.0	4	20	0.57	21.63	
CC 3	62.4946	61.9843	0.5103	5.0	4	20	0.47	18.30	
CC 4	51.0541	50.5611	0.4930	5.0	4	20	0.72	29.03	DIED DAY 5
CC 5	30.6548	30.1474	0.5074	5.0	4	20	0.59	23.32	DIED DAY 4
CC 6	30.9219	30.4167	0.5052	5.0	4	20	0.57	22.74	
CC 7	30.9436	30.4502	0.4934	5.0	4	20	0.54	21.78	
MEAN			0.5017						

BRAIN

FILE A_A_BR1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/23/93

SAMPLE: BRAIN

GROUPS: PB (TX & NO TX)

RUN 1 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	6.8					6.8
0.10	17.2					17.2
0.30	50.8					50.8
0.50	80.0					80.0
0.70	104.4					104.4
1.00	131.8					131.8

RUN 2 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	7.2					7.2
0.1	18.0					18.0
0.3	48.7					48.7
0.5	79.4					79.4
0.7	105.2					105.2
1.00	136.2					136.2

RUN 3 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	6.4					6.4
0.1	17.0					17.0
0.3	48.8					48.8
0.5	77.8					77.8
0.7	106.2					106.2
1.00	137.0					137.0

FILE A_A_BR1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/23/93

SAMPLE: BRAIN

GROUPS: PB (TX & NO TX)

TI STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	4.4	3.7	2.9
0.05	6.8	7.2	6.4	11.2	10.6	10.0
0.10	17.2	18.0	17.0	18.0	17.6	17.0
0.30	50.8	48.7	48.8	45.2	45.4	45.3
0.50	80.0	79.4	77.6	72.3	73.3	73.6
0.70	104.4	105.2	108.2	99.5	101.2	101.9
1.00	131.6	136.2	137.0	140.3	142.9	144.3

Regression Output:	RUN 1
Constant	4.3918297
Std Err of Y Est	6.7664332
R Squared	0.9854400
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	135.87083
Std Err of Coef.	7.3859249

Regression Output:	RUN 3
Constant	2.9034042
Std Err of Y Est	5.3385231
R Squared	0.9915781
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	141.38723
Std Err of Coef.	5.8272844

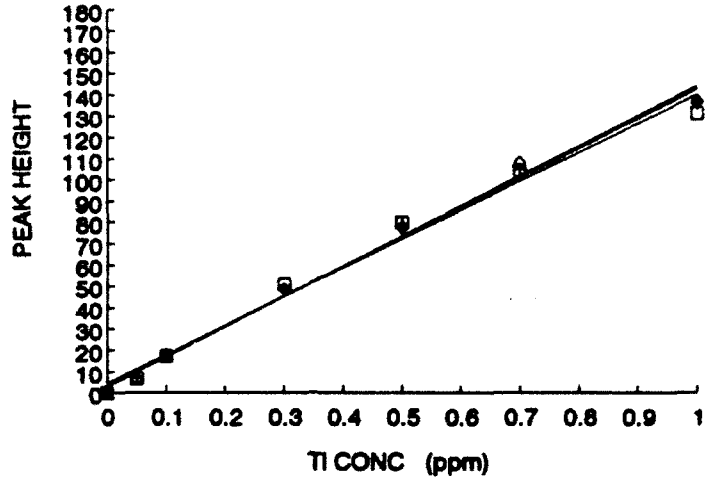
Regression Output:	RUN 2
Constant	3.6818297
Std Err of Y Est	5.1936828
R Squared	0.9917824
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	139.27083
Std Err of Coef.	5.6694018
Std Err of Coef.	5.6694018

Regression Output:	3 STD RUNS COMBINED
Constant	3.6523546
Std Err of Y Est	5.2356794
R Squared	0.9903825
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	138.84283
Std Err of Coef.	3.2998972
Std Err of Coef.	3.2998972

FILE A_A_BR1 THALLIUM ANTIDOTE STUDY DATE 2/23/93
PEAK HEIGHT WORKSHEET

SAMPLE: BRAIN

GROUPS: PB (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE Tl CONC (ppm)
TA 1	46.2	46.4			46.3	0.31
TA 2	40.0	44.2			42.1	0.28
TA 3	68.0	69.4			68.7	0.47
TA 4	40.0	40.4			40.2	0.26
TA 5	49.6	50.0			49.8	0.33
TA 6	50.2	51.4			50.8	0.34
TA 7	41.4	41.8			41.6	0.27
TA 8	31.2	37.4			34.3	0.22
TA 9	45.0	43.8			44.4	0.29
TA 10	42.8	47.0			44.8	0.30
CA 1	78.6	77.2			77.9	0.53
CA 2	71.0	71.6			71.3	0.48
CA 3	85.8	79.8			82.8	0.57
CA 4	51.8	51.8			51.8	0.35
CA 5	54.2	54.4			54.3	0.36
CA 6	93.2	92.6			92.9	0.64
CA 7	71.4	71.8			71.6	0.48

Tl CONC = (y - b) / m WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/22/93

FILE: A_A_BR2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: BRAIN
PB

DATE ANALYZED: 2/23/93

PATH: c:\data\lotus2.3
a:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	Tl CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A – B			D x E		F x G / C	
TA 1	30.4389	29.9426	0.4988	5.0	1	5	0.31	3.1	
TA 2	30.8307	30.3272	0.5035	5.0	1	5	0.28	2.7	
TA 3	31.0311	30.5108	0.5203	5.0	1	5	0.47	4.5	
TA 4	30.5922	30.0157	0.5765	5.0	1	5	0.26	2.6	
TA 5	30.8488	30.1582	0.4916	5.0	1	5	0.33	3.4	
TA 6	30.7783	30.2689	0.5094	5.0	1	5	0.34	3.3	
TA 7	30.9268	30.4276	0.4991	5.0	1	5	0.27	2.7	
TA 8	30.7989	30.3080	0.4909	5.0	1	5	0.22	2.2	
TA 9	30.7302	30.2197	0.5105	5.0	1	5	0.29	2.9	
TA 10	30.9467	30.4296	0.5171	5.0	1	5	0.30	2.9	
CA 1	31.4082	30.9122	0.4960	5.0	2	10	0.53	10.8	
CA 2	30.9514	30.4733	0.4781	5.0	2	10	0.49	10.2	
CA 3	25.7861	25.3078	0.4783	5.0	2	10	0.57	11.9	
CA 4	29.1204	28.6413	0.4791	5.0	2	10	0.35	7.2	
CA 5	26.4511	25.9479	0.5032	5.0	2	10	0.36	7.2	
CA 6	30.9212	30.4221	0.4991	5.0	2	10	0.64	12.9	DIED DAY 4
CA 7	30.6289	30.1270	0.5019	5.0	2	10	0.49	9.8	
MEAN			0.4969						

FILE A_B_BR1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/24/93

SAMPLE: BRAIN

GROUPS: DMPS (TX & NO TX)

RUN 1 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	8.0					8.0
0.10	22.2					22.2
0.30	70.2					70.2
0.50	105.2					105.2
0.70	129.2					129.2
1.00	166.8	168.0				167.4

RUN 2 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	8.2					8.2
0.1	23.2					23.2
0.3	67.6					67.6
0.5	92.6					92.6
0.7	127.0					127.0
1.00	167.6	168.6				168.1

RUN 3 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	9.2					9.2
0.1	22.4					22.4
0.3	69.2					69.2
0.5	94.8					94.8
0.7	130.2					130.2
1.00	169.6	172.0				170.8

FILE A_B_BR1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/24/93

SAMPLE: BRAIN

GROUPS: DMPS (TX & NO TX)

Tl STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	5.9	5.5	3.8
0.05	8.0	8.2	9.2	14.4	13.9	12.5
0.10	22.2	23.2	22.4	23.0	22.4	21.2
0.30	70.2	67.8	59.2	67.0	58.2	55.9
0.50	96.5	92.8	94.8	91.0	90.1	90.8
0.70	129.2	127.0	130.2	125.1	123.6	125.3
1.00	167.4	168.1	170.8	176.1	174.7	177.3

Regression Output:	RUN 1
Constant	5.9346957
Std Err of Y Est	8.5434764
R Squared	0.9852083
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	170.17276
Std Err of Coef.	9.256628

Regression Output:	RUN 3
Constant	3.8451914
Std Err of Y Est	4.9549449
R Squared	0.9951626
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	173.46553
Std Err of Coef.	5.4085881

Regression Output:	RUN 2
Constant	5.4507859
Std Err of Y Est	7.0984404
R Squared	0.9896367
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	169.28212
Std Err of Coef.	7.7461453

Regression Output:	3 STD RUNS COMBINED
Constant	5.3818586
Std Err of Y Est	7.0182780
R Squared	0.9875109
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	171.43480
Std Err of Coef.	4.4229786

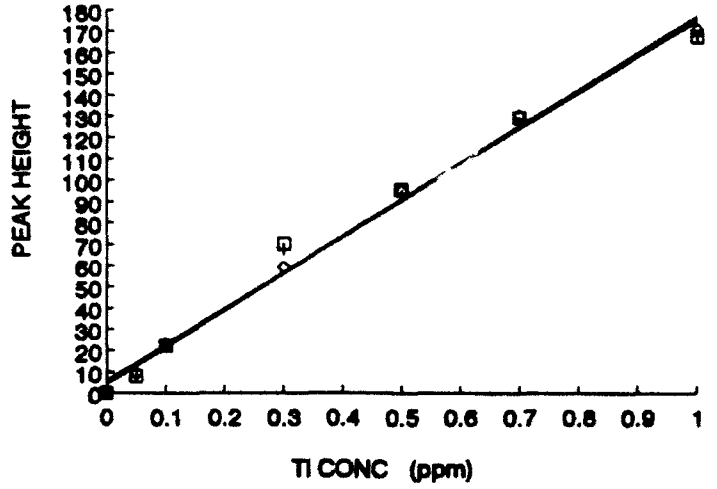
FILE A_B_BR1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/24/93

SAMPLE: BRAIN

GROUPS: DMPS (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE TI CONC (ppm)
TB 1	94.0	87.8			90.9	0.50
TB 2	105.6	105.0			105.3	0.58
TB 3	82.4	82.8			82.6	0.45
TB 4	89.6	87.0			88.3	0.48
TB 5	100.0	98.8			99.4	0.55
TB 6	84.8	85.2			85.0	0.35
TB 7	84.6	88.2			86.4	0.47
TB 8	56.0	65.0			60.5	0.32
TB 9	77.6	76.2			77.0	0.42
TB 10	79.4	78.0			78.7	0.43
CB 1	87.6	78.6			83.2	0.46
CB 2	87.6	74.8			81.2	0.44
CB 3	115.2	117.8			116.5	0.65
CB 4	96.4	89.4			92.9	0.51
CB 5	70.6	68.0			69.3	0.37
CB 6	95.8	97.4			96.6	0.53
CB 7	84.0	74.8			79.4	0.43

TI CONC = (y - b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/23/93

FILE: A_B_BR2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: BRAIN
DMPS

DATE ANALYZED: 2/24/93

PATH: c:\data\lotus2.3
s:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	Tl CONC ug Tl/g tissue - (wet wt) (H)	COMMENTS
FORMULA			A – B			D x E		F x G / C	
TB 1	30.8623	30.3592	0.5231	5.0	2	10	0.50	9.54	
TB 2	31.0075	30.5262	0.4813	5.0	2	10	0.58	12.11	
TB 3	30.1049	29.5919	0.5130	5.0	2	10	0.45	8.77	
TB 4	30.2180	29.7154	0.5026	5.0	2	10	0.48	9.53	
TB 5	30.3247	29.8139	0.5108	5.0	2	10	0.55	10.74	
TB 6	30.8871	30.4166	0.4705	5.0	2	10	0.35	7.39	
TB 7	30.2198	29.7384	0.4814	5.0	2	10	0.47	9.82	
TB 8	30.8106	30.3389	0.4717	5.0	2	10	0.32	6.82	
TB 9	30.8349	30.3345	0.5004	5.0	2	10	0.42	8.35	
TB 10	30.4820	29.9702	0.5118	5.0	2	10	0.43	8.38	
CB 1	31.4223	30.9462	0.4761	5.0	2	10	0.45	9.54	
CB 2	30.5968	30.1246	0.4722	5.0	2	10	0.44	9.37	
CB 3	28.7782	28.2961	0.4821	5.0	2	10	0.66	13.46	DIED DAY 5
CB 4	30.5486	30.0425	0.5063	5.0	2	10	0.51	10.09	
CB 5	30.3294	29.8592	0.4702	5.0	2	10	0.37	7.93	
CB 6	30.3547	29.8436	0.5111	5.0	2	10	0.53	10.41	
CB 7	30.8296	30.1473	0.4823	5.0	2	10	0.43	8.95	
MEAN			0.4922						

FILE A_C_BR1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/25/93

SAMPLE: BRAIN

GROUPS: PB + DMPS (TX & NO TX)

RUN 1 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	7.8					7.8
0.10	22.6					22.6
0.30	65.8					65.8
0.50	91.6					91.6
0.70	126.2					126.2
1.00	155.4					155.4

RUN 2 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	7.8					7.8
0.1	24.2					24.2
0.3	64.4					64.4
0.5	92.6					92.6
0.7	126.2					126.2
1.00	156.8	151.6				154.2

RUN 3 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	8.8					8.8
0.1	22.6					22.6
0.3	64.6					64.6
0.5	88.0					88.0
0.7	124.0					124.0
1.00	153.6	153.2				153.4

FILE A_C_BR1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/25/93

SAMPLE: BRAIN

GROUPS: PB + DMPS (TX & NO TX)

Tl STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	6.5	6.9	6.6
0.05	7.8	7.8	8.8	14.5	14.8	14.4
0.10	22.6	24.2	22.8	22.5	22.8	22.2
0.30	65.8	64.4	64.6	54.5	54.5	53.6
0.50	91.6	92.6	88.0	86.5	86.3	85.0
0.70	126.2	126.2	124.0	118.5	118.1	116.3
1.00	156.4	154.2	153.4	166.4	166.8	163.4

Regression Output:	RUN 1
Constant	6.5114993
Std Err of Y Est	9.2015724
R Squared	0.9806610
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	159.93191
Std Err of Coef.	10.044009

Regression Output:	RUN 3
Constant	6.5510636
Std Err of Y Est	8.5199590
R Squared	0.9827167
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	156.80851
Std Err of Coef.	9.2999923

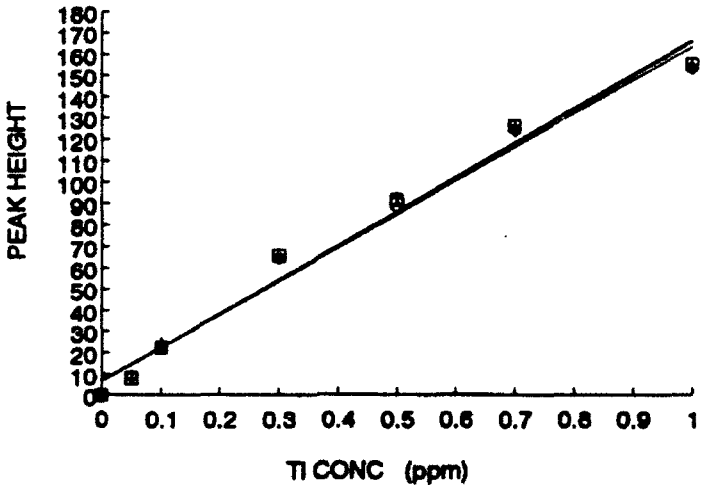
Regression Output:	RUN 2
Constant	6.8662978
Std Err of Y Est	9.3537007
R Squared	0.9797656
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	158.86638
Std Err of Coef.	10.210066

Regression Output:	3 STD RUNS COMBINED
Constant	6.6466170
Std Err of Y Est	8.0567647
R Squared	0.9806742
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	158.53590
Std Err of Coef.	5.0787043

FILE A_C_BR1 THALLIUM ANTIDOTE STUDY DATE 2/25/93
PEAK HEIGHT WORKSHEET

SAMPLE: BRAIN

GROUPS: PB + DMPS (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE TI CONC (ppm)
TC 1	51.2	51.6			51.4	0.28
TC 2	53.4	48.2			50.8	0.28
TC 3	45.0	44.6			44.8	0.24
TC 4	68.2	66.4			67.3	0.38
TC 5	66.0	78.0			78.0	0.42
TC 6	66.2	66.4			66.3	0.38
TC 7	61.4	61.2			61.3	0.34
TC 8	43.4	45.4			44.4	0.24
TC 9	57.8	54.2			56.0	0.31
TC 10	43.6	44.4			44.0	0.24
CC 1	87.2	87.4			87.3	0.51
CC 2	75.2	79.2			77.2	0.45
CC 3	80.8	81.8			81.2	0.47
CC 4	114.8	113.0			113.9	0.66
CC 5	119.4	118.8			119.1	0.71
CC 6	66.8	68.0			67.4	0.38
CC 7	70.2	70.0			70.1	0.40

TI CONC = (y - b) / m WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/24/93

FILE: A_C_BR2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: BRAIN
PB + DMPS

DATE ANALYZED: 2/25/93

PATH: c:\data\lotus2.3
a:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	TI CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A - B			D x E		F x G / C	
TC 1	59.4534	58.9563	0.4971	5.0	1	5	0.28	2.84	
TC 2	60.3807	59.8784	0.5023	5.0	1	5	0.28	2.77	
TC 3	62.5863	62.0759	0.5104	5.0	1	5	0.24	2.36	
TC 4	60.2441	59.7559	0.4882	5.0	1	5	0.38	3.92	
TC 5	62.1248	61.6232	0.5016	5.0	1	5	0.42	4.17	
TC 6	60.9309	60.4459	0.4850	5.0	1	5	0.38	3.88	
TC 7	58.4926	57.9643	0.4983	5.0	1	5	0.34	3.46	
TC 8	58.7482	58.2456	0.5026	5.0	1	5	0.24	2.37	
TC 9	63.1529	62.6526	0.5003	5.0	1	5	0.31	3.11	
TC 10	62.4903	61.9818	0.4985	5.0	1	5	0.24	2.36	
CC 1	62.1171	61.6241	0.4930	5.0	2	10	0.51	10.32	
CC 2	62.9526	62.4492	0.5034	5.0	2	10	0.45	8.84	
CC 3	61.4210	60.9108	0.5102	5.0	2	10	0.47	9.22	
CC 4	62.4098	61.9112	0.4986	5.0	2	10	0.68	13.57	DIED DAY 5
CC 5	49.3086	48.8104	0.4981	5.0	2	10	0.71	14.24	DIED DAY 4
CC 6	49.7932	49.3022	0.4910	5.0	2	10	0.38	7.80	
CC 7	62.7686	62.2719	0.4967	5.0	2	10	0.40	8.06	
MEAN			0.4965						

BLOOD

FILE A_A_BL1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/26/03

SAMPLE: BLOOD

GROUPS: PB (TX & NO TX)

RUN 1 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	3.2					3.2
0.10	13.2					13.2
0.30	46.8					46.8
0.50	76.6					76.6
0.70	102.6					102.6
1.00	130.8	130.6				130.7

RUN 2 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.4					5.4
0.1	13.4					13.4
0.3	46.0					46.0
0.5	75.4					75.4
0.7	104.8					104.8
1.00	139.2	135.2				137.2

RUN 3 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	3.8					3.8
0.1	12.0					12.0
0.3	43.8					43.8
0.5	75.4					75.4
0.7	105.2					105.2
1.00	139.0	141.0				140.0

FILE A_A_BL1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/26/93

SAMPLE: BLOOD

GROUPS: PB (TX & NO TX)

Tl STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	1.4	0.9	−0.7
0.05	3.2	5.4	3.8	8.2	8.0	6.6
0.10	13.2	13.4	12.0	15.1	15.1	13.8
0.30	46.8	48.0	43.8	42.5	43.5	42.9
0.50	76.6	75.4	75.4	70.0	71.8	72.0
0.70	102.6	104.8	105.2	97.4	100.2	101.0
1.00	130.7	137.2	140.0	138.5	142.7	144.6

Regression Output:	RUN 1
Constant	1.3848085
Std Err of Y Est	6.0300646
R Squared	0.9896122
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	137.13446
Std Err of Coef.	6.5821360

Regression Output:	RUN 3
Constant	−0.887148
Std Err of Y Est	3.5479822
R Squared	0.9964903
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	145.28680
Std Err of Coef.	3.8724854

Regression Output:	RUN 2
Constant	0.9324255
Std Err of Y Est	4.0405485
R Squared	0.9951836
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	141.76340
Std Err of Coef.	4.4104784

Regression Output:	3 STD RUNS COMBINED
Constant	0.5433617
Std Err of Y Est	4.3586803
R Squared	0.9928602
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	141.39499
Std Err of Coef.	2.7468786

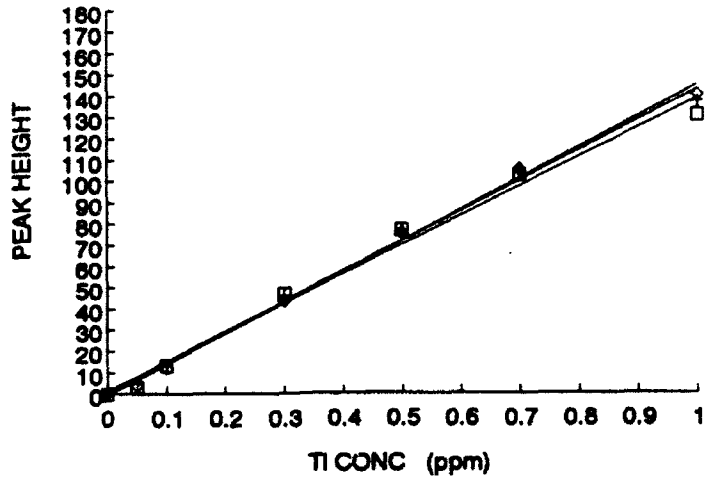
FILE A_A_BL1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/26/93

SAMPLE: BLOOD

GROUPS: PB (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE TI CONC (ppm)
TA 1	77.0	77.6			77.3	0.54
TA 2	72.4	66.6			69.0	0.48
TA 3	48.6	45.2			46.9	0.33
TA 4	49.2	51.0			49.8	0.35
TA 5	94.0	92.8			93.4	0.66
TA 6	76.0	76.0			76.0	0.53
TA 7	70.4	73.2			71.8	0.50
TA 8	75.4	73.4			74.4	0.52
TA 9	64.0	57.2			60.6	0.42
TA 10	49.2	49.0			49.1	0.34
CA 1	45.0	45.2			45.1	0.32
CA 2	67.6	68.8			68.2	0.48
CA 3	45.2	45.6			45.4	0.32
CA 4	43.0	44.8			43.9	0.31
CA 5	40.2	37.8			39.0	0.27
CA 6	76.0	74.2			75.1	0.53
CA 7	50.0	47.4			48.7	0.34

TI CONC = (y - b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

FILE: A_A_BL2

THALLIUM ANTIDOTE STUDY
TI ANALYSIS WORKSHEET

DATE ANALYZED: 2/26/93

SAMPLE: BLOOD
PB

SAMPLE	VOLUME BLOOD USED (ml) (A)	VOLUME MIBK USED (ml) (B)	INITIAL CONC FACTOR (D)	DILUTION FACTOR (E)	NET CONC FACTOR (F)	TI CONC SAMPLE ANALYZED (ug/ml) (G)	BLOOD TI CONC (ug/ml) (H)	COMMENTS
FORMULA			A / B		D / E		G / F	
TA 1	4.0	2.0	2	1	2	0.54	0.27	
TA 2	4.0	2.0	2	1	2	0.48	0.24	
TA 3	4.0	2.0	2	1	2	0.33	0.16	
TA 4	4.0	2.0	2	1	2	0.35	0.17	
TA 5	4.0	2.0	2	1	2	0.66	0.33	
TA 6	4.0	2.0	2	1	2	0.53	0.27	
TA 7	4.0	2.0	2	1	2	0.50	0.25	
TA 8	4.0	2.0	2	1	2	0.52	0.26	
TA 9	4.0	2.0	2	1	2	0.42	0.21	
TA 10	4.0	2.0	2	1	2	0.34	0.17	
CA 1	4.0	2.0	2	8	0.25	0.32	1.26	
CA 2	4.0	2.0	2	8	0.25	0.48	1.91	
CA 3	4.0	2.0	2	8	0.25	0.32	1.27	
CA 4	4.0	2.0	2	8	0.25	0.31	1.23	
CA 5	4.0	2.0	2	8	0.25	0.27	1.09	
CA 6	4.0	2.0	2	8	0.25	0.53	2.11	DIED DAY 4
CA 7	4.0	2.0	2	8	0.25	0.34	1.36	

Column (D): TI content in 4 ml whole blood extracted into 2 ml MIBK.
Column (E): Dilution required to put sample in linear range of calibration curve (if necessary).

FILE A_B_BL1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/27/89

SAMPLE: BLOOD

GROUPS: DMPS (TX & NO TX)

RUN 1 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	11.2	12.2				11.7
0.10	24.6					24.6
0.30	66.0					66.0
0.50	79.4					79.4
0.70	119.6	120.6				120.1
1.00	140.8	150.0				145.4

RUN 2 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	13.8					13.8
0.1	24.0					24.0
0.3	55.2					55.2
0.5	89.4					89.4
0.7	116.8					116.8
1.00	143.0	143.8				143.4

RUN 3 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	10.2					10.2
0.1	23.0					23.0
0.3	53.8					53.8
0.5	91.0					91.0
0.7	115.2					115.2
1.00	142.8	140.8				141.8

FILE A_B_BL1 THALLIUM ANTIDOTE STUDY DATE 2/27/93
PEAK HEIGHT WORKSHEET

SAMPLE: BLOOD

GROUPS: DMPS (TX & NO TX)

Tl STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	8.5	8.2	7.0
0.05	11.7	13.8	10.2	15.8	15.5	14.3
0.10	24.6	24.0	23.0	23.2	22.8	21.6
0.30	66.0	55.2	53.8	52.4	51.8	50.7
0.50	79.4	89.4	91.0	81.8	80.9	79.8
0.70	120.1	116.8	115.2	110.9	109.9	108.9
1.00	145.4	143.4	141.8	154.7	153.5	152.6

Regression Output:	RUN 1
Constant	8.5321276
Std Err of Y Est	9.5336146
R Squared	0.9752988
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	146.21702
Std Err of Coef.	10.408451

Regression Output:	RUN 3
Constant	7.0177021
Std Err of Y Est	8.4731220
R Squared	0.9802271
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	145.61361
Std Err of Coef.	9.2488672

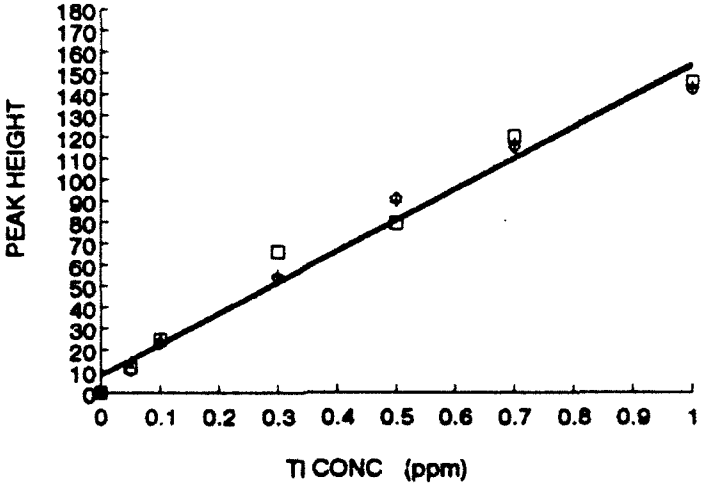
Regression Output:	RUN 2
Constant	8.2194042
Std Err of Y Est	7.8209251
R Squared	0.9830343
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	145.20723
Std Err of Coef.	8.5388693

Regression Output:	3 STD RUNS COMBINED
Constant	7.9230780
Std Err of Y Est	7.7134602
R Squared	0.9782918
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	145.71282
Std Err of Coef.	4.8611030

FILE A_B_BL1 THALLIUM ANTIDOTE STUDY DATE 2/27/93
PEAK HEIGHT WORKSHEET

SAMPLE: BLOOD

GROUPS: DMPS (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE Tl CONC (ppm)
TB 1	58.2	61.8			60.0	0.36
TB 2	60.6	61.4			61.0	0.36
TB 3	62.4	63.8			63.1	0.38
TB 4	90.0	89.2			89.6	0.56
TB 5	82.6	81.8			82.2	0.51
TB 6	54.0	48.8			51.4	0.30
TB 7	51.2	46.8			49.0	0.28
TB 8	54.0	58.6			56.3	0.33
TB 9	57.2	58.2			57.7	0.34
TB 10	58.4	59.2			58.8	0.35
CB 1	82.0	80.2			81.1	0.50
CB 2	137.4	130.0			133.7	0.86
CB 3	140.0	140.6			140.3	0.91
CB 4	66.8	71.8			69.3	0.42
CB 5	111.8	111.6			111.7	0.71
CB 6	141.4	145.2			143.3	0.93
CB 7	136.2	140.2			138.2	0.89

Tl CONC = (y - b) / m WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

FILE: A_B_BL2

THALLIUM ANTIDOTE STUDY
TI ANALYSIS WORKSHEET

DATE ANALYZED: 2/27/93

SAMPLE: BLOOD
DMPS

SAMPLE	VOLUME BLOOD USED (ml) (A)	VOLUME MIBK USED (ml) (B)	INITIAL CONC FACTOR (D)	DILUTION FACTOR (E)	NET CONC FACTOR (F)	TI CONC SAMPLE ANALYZED (ug/ml) (G)	BLOOD TI CONC (ug/ml) (H)	COMMENTS
FORMULA							G / F	
TB 1	7.5	1.5	5	–	5	0.36	0.071	
TB 2	7.5	1.5	5	–	5	0.36	0.073	
TB 3	7.5	1.5	5	–	5	0.38	0.076	
TB 4	7.5	1.5	5	–	5	0.56	0.112	
TB 5	7.5	1.5	5	–	5	0.51	0.102	
TB 6	7.5	1.5	5	–	5	0.30	0.060	
TB 7	7.5	1.5	5	–	5	0.28	0.056	
TB 8	7.5	1.5	5	–	5	0.33	0.066	
TB 9	7.5	1.5	5	–	5	0.34	0.068	
TB 10	7.5	1.5	5	–	5	0.35	0.070	
CB 1	2.0	4.0	–	2	0.50	0.50	1.00	
CB 2	2.0	4.0	–	2	0.50	0.86	1.73	
CB 3	2.0	4.0	–	2	0.50	0.91	1.82	
CB 4	2.0	4.0	–	2	0.50	0.42	0.84	
CB 5	2.0	4.0	–	2	0.50	0.71	1.42	
CB 6	2.0	4.0	–	2	0.50	0.93	1.86	DIED DAY 4
CB 7	2.0	4.0	–	2	0.50	0.89	1.79	

Column (D): TI content in 7.5 ml whole blood extracted into 1.5 ml MIBK. Applicable to TB group only.
Column (E): Dilution required to put sample in linear range of calibration curve (if necessary). Applicable to CB group only.

FILE A_C_BL1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/28/93

SAMPLE: BLOOD

GROUPS: PB + DMPS (TX & NO TX)

RUN 1 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	10.0					10.0
0.10	20.0					20.0
0.30	54.4					54.4
0.50	86.2					86.2
0.70	115.8					115.8
1.00	144.8	141.8				143.2

RUN 2 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	9.0					9.0
0.1	22.6					22.6
0.3	49.8					49.8
0.5	89.8					89.8
0.7	119.0					119.0
1.00	149.4	147.2				148.3

RUN 3 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	9.8					9.8
0.1	18.4					18.4
0.3	49.6					49.6
0.5	81.2					81.2
0.7	123.6					123.6
1.00	138.4	143.4				140.9

FILE A_C_BL1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/26/93

SAMPLE: BLOOD

GROUPS: PB + DMPS (TX & NO TX)

Tl STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	5.8	3.1	4.2
0.05	10.0	9.0	9.8	12.9	10.5	11.8
0.10	20.0	22.6	18.4	20.3	18.0	19.0
0.30	54.4	49.8	49.8	49.7	48.0	48.8
0.50	85.2	69.8	81.2	78.1	77.9	78.6
0.70	115.8	119.0	123.8	106.5	107.9	108.3
1.00	143.2	148.3	140.9	152.8	152.8	153.0

Regression Output:	RUN 1	
Constant		5.5563404
Std Err of Y Est		6.9440102
R Squared		0.9868910
No. of Observations		7
Degrees of Freedom		5
X Coefficient(s)	147.05872	
Std Err of Coef.	7.5797587	

Regression Output:	RUN 3	
Constant		4.1566723
Std Err of Y Est		9.0276782
R Squared		0.9785491
No. of Observations		7
Degrees of Freedom		5
X Coefficient(s)	148.82287	
Std Err of Coef.	9.8540859	

Regression Output:	RUN 2	
Constant		3.0613191
Std Err of Y Est		7.0604102
R Squared		0.9869322
No. of Observations		7
Degrees of Freedom		5
X Coefficient(s)	149.76255	
Std Err of Coef.	7.7068165	

Regression Output:	3 STD RUNS COMBINED	
Constant		4.2991773
Std Err of Y Est		6.9151637
R Squared		0.9839102
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	148.54808	
Std Err of Coef.	4.3579970	

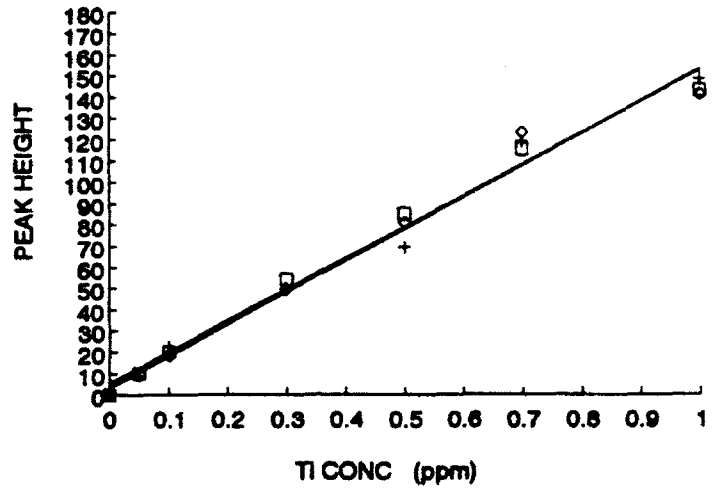
FILE A_C_BL1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 2/28/93

SAMPLE: BLOOD

GROUPS: PB + DMPS (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE Tl CONC (ppm)
TC 1	23.6	34.0			28.8	0.17
TC 2	42.6	45.6			44.1	0.27
TC 3	52.2	53.2			52.7	0.33
TC 4	48.2	44.6			46.4	0.28
TC 5	48.0	48.8			48.4	0.30
TC 6	27.8	40.2			33.9	0.20
TC 7	31.6	36.0			34.8	0.21
TC 8	34.2	29.8			31.9	0.19
TC 9	28.6	27.8			28.2	0.16
TC 10	45.2	46.0			45.6	0.28
CC 1	131.8	129.6			130.7	0.85
CC 2	71.2	80.0			75.6	0.46
CC 3	80.0	85.6			82.8	0.53
CC 4	130.0	132.0			131.0	0.85
CC 5	139.4	140.4			139.9	0.91
CC 6	116.0	114.8			116.4	0.75
CC 7	106.8	101.4			105.1	0.68

Tl CONC = (y - b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

FILE: A_C_BL2

THALLIUM ANTIDOTE STUDY
TI ANALYSIS WORKSHEET

DATE ANALYZED: 2/28/93

SAMPLE: BLOOD
PB + DMPS

SAMPLE	VOLUME BLOOD USED (ml) (A)	VOLUME MIBK USED (ml) (B)	INITIAL CONC FACTOR (D)	DILUTION FACTOR (E)	NET CONC FACTOR (F)	TI CONC SAMPLE ANALYZED (ug/ml) (G)	BLOOD TI CONC (ug/ml) (H)	COMMENTS
FORMULA							G / F	
TC 1	7.5	1.5	5	–	5	0.17	0.033	
TC 2	7.5	1.5	5	–	5	0.27	0.054	
TC 3	7.5	1.5	5	–	5	0.33	0.065	
TC 4	7.5	1.5	5	–	5	0.28	0.057	
TC 5	7.5	1.5	5	–	5	0.30	0.059	
TC 6	7.5	1.5	5	–	5	0.20	0.040	
TC 7	7.5	1.5	5	–	5	0.21	0.041	
TC 8	7.5	1.5	5	–	5	0.19	0.037	
TC 9	7.5	1.5	5	–	5	0.16	0.032	
TC 10	7.5	1.5	5	–	5	0.28	0.056	
CC 1	2.0	4.0	–	2	0.50	0.85	1.70	
CC 2	2.0	4.0	–	2	0.50	0.48	0.96	
CC 3	2.0	4.0	–	2	0.50	0.53	1.06	
CC 4	2.0	4.0	–	2	0.50	0.85	1.71	
CC 5	2.0	4.0	–	2	0.50	0.91	1.83	
CC 6	2.0	4.0	–	2	0.50	0.75	1.51	DIED DAY 4
CC 7	2.0	4.0	–	2	0.50	0.68	1.36	

Column (D): TI content in 7.5 ml whole blood extracted into 1.5 ml MIBK. Applicable to TC group only.
Column (E): Dilution required to put sample in linear range of calibration curve (if necessary). Applicable to CC group only.

FECES

FILE A_A_F1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 3/1/93

SAMPLE: FECES

GROUPS: PB (TX & NO TX)

RUN 1 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	7.0					7.0
0.10	18.8					18.8
0.30	58.8					58.8
0.50	89.0					89.0
0.70	106.6					106.6
1.00	149.4	149.2				149.3

RUN 2 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	7.8					7.8
0.1	20.0					20.0
0.3	59.2					59.2
0.5	88.2					88.2
0.7	110.6					110.6
1.00	148.8	154.6				151.7

RUN 3 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	7.6					7.6
0.1	19.8					19.8
0.3	56.6					56.6
0.5	84.8					84.8
0.7	111.0					111.0
1.00	156.2	150.2				153.2

FILE A_A_F1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 3/1/93

SAMPLE: FECES

GROUPS: PB (TX & NO TX)

TI STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	4.7	4.9	3.8
0.05	7.0	7.8	7.6	12.2	12.5	11.5
0.10	18.8	20.0	19.8	19.7	20.1	19.1
0.30	58.8	59.2	56.8	49.8	50.5	49.8
0.50	89.0	88.2	84.8	79.9	81.0	80.5
0.70	108.6	110.6	111.0	110.0	111.4	111.2
1.00	149.3	151.7	153.2	156.2	157.1	157.2

Regression Output:	RUN 1
Constant	4.6570638
Std Err of Y Est	7.0597834
R Squared	0.9870654
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	150.52851
Std Err of Coef.	7.7061323

Regression Output:	RUN 3
Constant	3.7668510
Std Err of Y Est	4.6976727
R Squared	0.9944416
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	153.36680
Std Err of Coef.	5.1277618

Regression Output:	RUN 2
Constant	4.8788510
Std Err of Y Est	6.3649233
R Squared	0.9896806
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	152.20680
Std Err of Coef.	6.9476552

Regression Output:	3 STD RUNS COMBINED
Constant	4.4442563
Std Err of Y Est	5.4690926
R Squared	0.9903294
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	152.03404
Std Err of Coef.	3.4486702

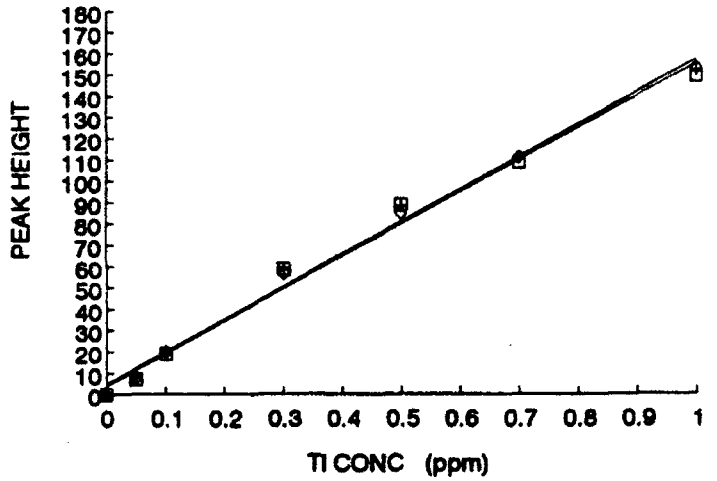
FILE A_A_F1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 3/1/93

SAMPLE: FECES

GROUPS: PB (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE TI CONC (ppm)
TA 1	78.2	78.0			78.1	0.48
TA 2	68.4	69.4			68.9	0.42
TA 3	69.0	70.0			69.5	0.43
TA 4	49.4	50.2			49.8	0.30
TA 5	57.8	59.6			58.7	0.36
TA 6	57.2	59.6			58.4	0.35
TA 7	89.8	86.0			87.9	0.55
TA 8	57.2	60.4			58.8	0.36
TA 9	59.8	60.0			59.9	0.36
TA 10	59.4	57.8			58.6	0.36
CA 1	61.2	60.0			60.6	0.37
CA 2	48.2	43.8			46.0	0.27
CA 3	60.8	61.2			61.0	0.37
CA 4	62.6	62.0			62.3	0.38
CA 5	59.8	58.0			58.9	0.36
CA 6	45.0	50.0			47.5	0.28
CA 7	77.4	73.6			75.5	0.47

TI CONC = (y - b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y – INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 2/26/93

FILE: A_A_F2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: FECES
PB

DATE ANALYZED: 3/1/93

PATH: c:\data\lotus2.3
a:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	Tl CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A – B			D x E		F x G / C	
TA 1	30.9492	30.4501	0.4991	5.0	2	10	0.48	9.71	
TA 2	60.5125	30.0298	0.4827	5.0	2	10	0.42	8.78	
TA 3	30.3622	29.8583	0.5039	5.0	2	10	0.43	8.49	
TA 4	31.6609	31.1415	0.5194	5.0	2	10	0.30	5.74	
TA 5	30.8983	30.3898	0.5085	5.0	2	10	0.36	7.02	
TA 6	30.4818	29.9926	0.4892	5.0	2	10	0.35	7.25	
TA 7	31.0594	30.5573	0.5021	5.0	2	10	0.55	10.93	
TA 8	30.8007	30.2883	0.5124	5.0	2	10	0.36	6.96	
TA 9	30.9711	30.4906	0.4805	5.0	2	10	0.36	7.59	
TA 10	30.3195	29.7989	0.5206	5.0	2	10	0.36	6.84	
CA 1	31.1237	30.6307	0.4930	5.0	1	5	0.37	3.75	
CA 2	29.2156	28.7024	0.5132	5.0	1	5	0.27	2.66	
CA 3	30.8248	30.3110	0.5138	5.0	1	5	0.37	3.62	
CA 4	30.7167	30.2424	0.4743	5.0	1	5	0.38	4.01	
CA 5	30.9395	30.4459	0.4936	5.0	1	5	0.36	3.63	
CA 6	30.9021	30.4070	0.4951	5.0	1	5	0.28	2.86	DIED DAY 4
CA 7	30.9158	30.3895	0.5263	5.0	1	5	0.47	4.44	
MEAN			0.5016						

FILE A_B_F1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 3/2/93

SAMPLE: FECES

GROUPS: DMPS (TX & NO TX)

RUN 1 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	7.6					7.6
0.10	19.4					19.4
0.30	54.8					54.8
0.50	86.0					86.0
0.70	110.0					110.0
1.00	150.8	149.0				149.9

RUN 2 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	6.6					6.6
0.1	17.8					17.8
0.3	53.0					53.0
0.5	85.0					85.0
0.7	106.2					106.2
1.00	148.0	141.0				144.5

RUN 3 Tl STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.2					5.2
0.1	17.0					17.0
0.3	47.8					47.8
0.5	80.4					80.4
0.7	103.4					103.4
1.00	140.2	139.2				139.7

FILE A_B_F1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 3/2/93

SAMPLE: FECES

GROUPS: DMPS (TX & NO TX)

TI STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	3.9	3.6	2.2
0.05	7.6	6.6	5.2	11.5	10.9	9.4
0.10	19.4	17.8	17.0	19.0	18.2	16.5
0.30	54.8	53.0	47.6	49.2	47.5	45.0
0.50	86.0	85.0	80.4	79.4	76.8	73.5
0.70	110.0	106.2	103.4	109.6	106.1	102.0
1.00	149.9	144.5	139.7	154.9	150.1	144.8

Regression Output:	RUN 1
Constant	3.9299148
Std Err of Y Est	5.1041820
R Squared	0.9932403
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	151.01531
Std Err of Coef.	5.5714885

Regression Output:	RUN 3
Constant	2.2259148
Std Err of Y Est	4.5732652
R Squared	0.9939044
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	142.53531
Std Err of Coef.	4.9919643

Regression Output:	RUN 2
Constant	3.5506106
Std Err of Y Est	5.6451834
R Squared	0.9912326
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	146.50606
Std Err of Coef.	6.1620205

Regression Output:	3 STD RUNS COMBINED
Constant	3.2354468
Std Err of Y Est	5.1787206
R Squared	0.9906819
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	146.68624
Std Err of Coef.	3.2636752

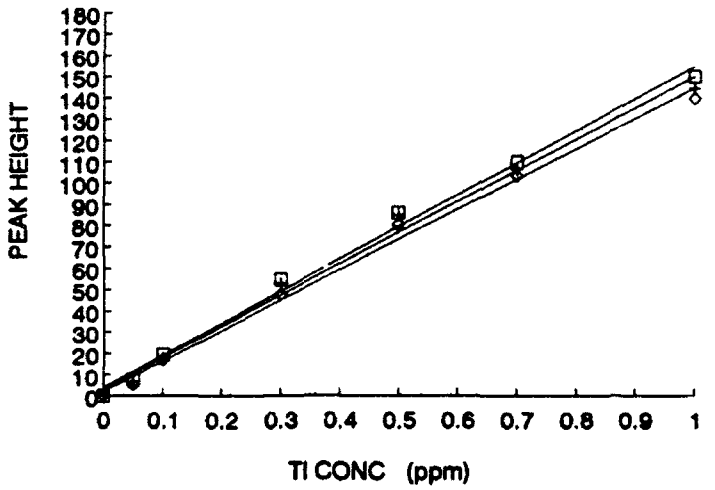
FILE A_B_F1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 3/2/93

SAMPLE: FECES

GROUPS: DMPS (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE TI CONC (ppm)
TB 1	57.4	56.8			57.1	0.37
TB 2	59.8	57.8			58.8	0.38
TB 3	52.0	50.2			51.1	0.33
TB 4	56.8	56.0			56.4	0.36
TB 5	44.2	41.2			42.7	0.27
TB 6	64.4	58.8			61.6	0.40
TB 7	56.0	55.6			55.8	0.36
TB 8	48.8	44.0			46.4	0.29
TB 9	33.4	35.8			34.6	0.21
TB 10	34.8	32.2			33.5	0.21
CB 1	49.8	53.6			51.7	0.33
CB 2	66.6	71.2			68.9	0.45
CB 3	46.8	51.8			49.3	0.31
CB 4	70.6	72.0			71.3	0.46
CB 5	41.2	46.2			43.7	0.28
CB 6	73.2	72.6			72.9	0.47
CB 7	72.8	72.2			72.5	0.47

TI CONC = (y - b) / m

WHERE y = AVERAGE PEAK HEIGHT
b = y - INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 3/1/93

FILE: A_B_F2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: FECES
DMPS

DATE ANALYZED: 3/2/93

PATH: c:\data\lotus2.3
a:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	Tl CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A – B			D x E		F x G / C	
TB 1	55.9016	55.3912	0.5104	5.0	1	5	0.37	3.60	
TB 2	53.4667	52.9460	0.5207	5.0	1	5	0.38	3.64	
TB 3	61.8249	61.2946	0.5303	5.0	1	5	0.33	3.08	
TB 4	58.9327	58.4631	0.4696	5.0	1	5	0.36	3.86	
TB 5	61.6638	61.1783	0.4855	5.0	1	5	0.27	2.77	
TB 6	72.5951	72.1182	0.4769	5.0	1	5	0.40	4.17	
TB 7	78.2065	77.7101	0.4964	5.0	1	5	0.36	3.61	
TB 8	18.8489	18.3298	0.5173	5.0	1	5	0.29	2.84	
TB 9	79.0937	78.5997	0.4940	5.0	1	5	0.21	2.16	
TB 10	81.9514	81.4733	0.4781	5.0	1	5	0.21	2.16	
CB 1	72.1988	71.7151	0.4837	5.0	1	5	0.33	3.42	
CB 2	72.3586	71.8404	0.5182	5.0	1	5	0.45	4.32	
CB 3	78.2993	77.8089	0.4904	5.0	1	5	0.31	3.20	DIED DAY 5
CB 4	81.2691	80.7721	0.5170	5.0	1	5	0.46	4.49	
CB 5	78.3095	77.8289	0.4806	5.0	1	5	0.28	2.87	
CB 6	81.5370	80.9892	0.5478	5.0	1	5	0.47	4.33	
CB 7	79.3104	78.8065	0.5039	5.0	1	5	0.47	4.69	
MEAN			0.5012						

FILE A_C_F1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 3/3/93

SAMPLE: FECES

GROUPS: PB + DMPS (TX & NO TX)

RUN 1 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	6.0					6.0
0.10	14.2					14.2
0.30	37.6					37.6
0.50	85.0					85.0
0.70	106.8					106.8
1.00	135.4	138.8				137.1

RUN 2 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	5.2					5.2
0.1	12.2					12.2
0.3	47.4					47.4
0.5	77.4					77.4
0.7	99.0					99.0
1.00	133.8	129.6				131.7

RUN 3 TI STDS (ppm)	PEAK HEIGHT DATA					AVERAGE PEAK HT
BLK	0					0.0
0.05	2.4					2.4
0.1	13.2					13.2
0.3	46.8					46.8
0.5	82.0					82.0
0.7	104.8					104.8
1.00	133.0	135.4				134.2

FILE A_C_F1 THALLIUM ANTIDOTE STUDY DATE 3/3/93
PEAK HEIGHT WORKSHEET

SAMPLE: FECES

GROUPS: PB + DMPS (TX & NO TX)

Tl STDS	PEAK HEIGHTS			DATA POINTS FOR LINEAR REGRESSION LINE		
	RUN 1	RUN 2	RUN 3	RUN 1	RUN 2	RUN 3
0	0	0	0	0.7	1.7	1.1
0.05	6.0	5.2	2.4	7.9	8.6	8.2
0.10	14.2	12.2	13.2	15.1	15.4	15.3
0.30	37.6	47.4	46.8	43.9	42.6	43.6
0.50	85.0	77.4	82.0	72.7	69.8	71.9
0.70	106.8	99.0	104.6	101.6	97.0	100.3
1.00	137.1	131.7	134.2	144.8	137.9	142.7

Regression Output:	RUN 1
Constant	0.6792765
Std Err of Y Est	7.5062647
R Squared	0.9840985
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	144.13021
Std Err of Coef.	8.1934906

Regression Output:	RUN 3
Constant	1.1422978
Std Err of Y Est	6.9665628
R Squared	0.9857821
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	141.58638
Std Err of Coef.	7.6043770

Regression Output:	RUN 2
Constant	1.7460851
Std Err of Y Est	5.4229028
R Squared	0.9906310
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	136.10468
Std Err of Coef.	5.9193893

Regression Output:	3 STD RUNS COMBINED
Constant	1.1892196
Std Err of Y Est	6.1317310
R Squared	0.9858522
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	140.60709
Std Err of Coef.	3.8642706

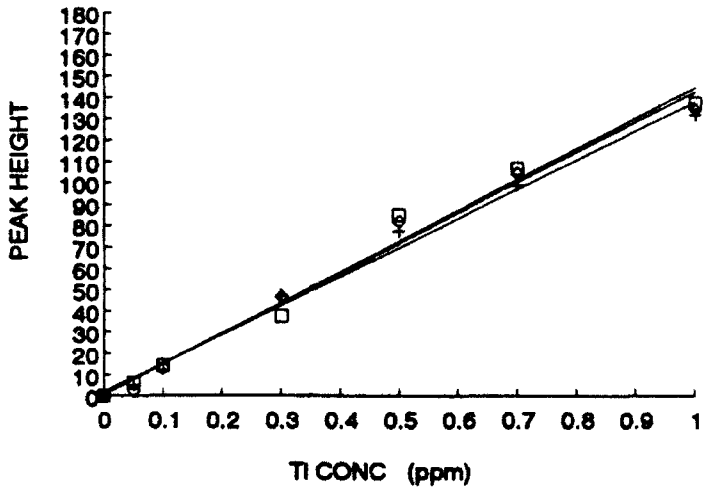
FILE A_C_F1

THALLIUM ANTIDOTE STUDY
PEAK HEIGHT WORKSHEET

DATE 3/3/93

SAMPLE: FECES

GROUPS: PB + DMPS (TX & NO TX)



SAMPLE ID	PEAK HEIGHT DATA				AVERAGE PEAK HT	SAMPLE TI CONC (ppm)
TC 1	102.2	101.0			101.6	0.71
TC 2	99.0	99.6			99.3	0.70
TC 3	84.2	83.2			83.7	0.59
TC 4	105.2	105.6			105.4	0.74
TC 5	124.2	126.2			126.2	0.89
TC 6	126.0	124.4			125.2	0.88
TC 7	107.6	108.2			108.9	0.75
TC 8	95.0	94.4			94.7	0.67
TC 9	95.2	97.0			96.1	0.68
TC 10	96.6	90.8			93.7	0.66
CC 1	49.6	48.8			49.2	0.34
CC 2	45.4	43.8			44.6	0.31
CC 3	45.0	45.0			45.0	0.31
CC 4	72.0	71.4			71.7	0.50
CC 5	69.2	66.2			67.7	0.47
CC 6	48.2	44.0			46.1	0.32
CC 7	50.6	50.4			50.5	0.35

TI CONC = (y − b) / m WHERE y = AVERAGE PEAK HEIGHT
b = y − INTERCEPT, COMBINED RUNS
m = SLOPE, COMBINED RUNS

DATE WET ASHED: 3/2/93

FILE: A_C_F2

THALLIUM ANTIDOTE STUDY
WET ASH DATA WORKSHEET

TISSUE TYPE: FECES
PB + DMPS

DATE ANALYZED: 3/3/93

PATH: c:\data\lotus2.3
a:\lotus

SAMPLE	BEAKER+ SAMPLE WT (g) (A)	BEAKER TARE WT (g) (B)	NET WT SAMPLE (g) (C)	DILUTION FACTOR (sample extracted into 5 ml MIBK) (D)	ADDITIONAL DILUTION FACTOR (to put sample in linear range of cal curve) (E)	TOTAL DILUTION FACTOR (F)	SAMPLE CONC (ppm) (G)	Tl CONC ug Tl/g tissue (wet wt) (H)	COMMENTS
FORMULA			A – B			D x E		F x G / C	
TC 1	60.9017	60.4110	0.4907	5.0	1	5	0.71	7.28	
TC 2	49.5101	49.0231	0.4870	5.0	1	5	0.70	7.16	
TC 3	63.1214	62.6197	0.5017	5.0	1	5	0.59	5.85	
TC 4	62.4931	61.9842	0.5089	5.0	1	5	0.74	7.28	
TC 5	57.0524	56.5642	0.4882	5.0	1	5	0.89	9.11	
TC 6	60.5919	60.0879	0.5040	5.0	1	5	0.86	8.75	
TC 7	61.9762	61.4860	0.4902	5.0	1	5	0.75	7.67	
TC 8	50.5289	50.0128	0.5161	5.0	1	5	0.67	6.44	
TC 9	63.2498	62.7455	0.5043	5.0	1	5	0.88	8.69	
TC 10	56.3072	55.8286	0.4786	5.0	1	5	0.66	6.87	
CC 1	60.6436	60.1374	0.5062	5.0	1	5	0.34	3.37	
CC 2	49.2093	48.6773	0.5320	5.0	1	5	0.31	2.90	
CC 3	49.9745	49.4833	0.4912	5.0	1	5	0.31	3.17	
CC 4	60.2762	59.7826	0.4936	5.0	1	5	0.50	5.08	DIED DAY 5
CC 5	62.1355	61.6139	0.5216	5.0	1	5	0.47	4.53	DIED DAY 4
CC 6	61.9667	61.4760	0.5107	5.0	1	5	0.32	3.13	
CC 7	62.5014	61.9833	0.5181	5.0	1	5	0.35	3.38	
MEAN			0.5025						